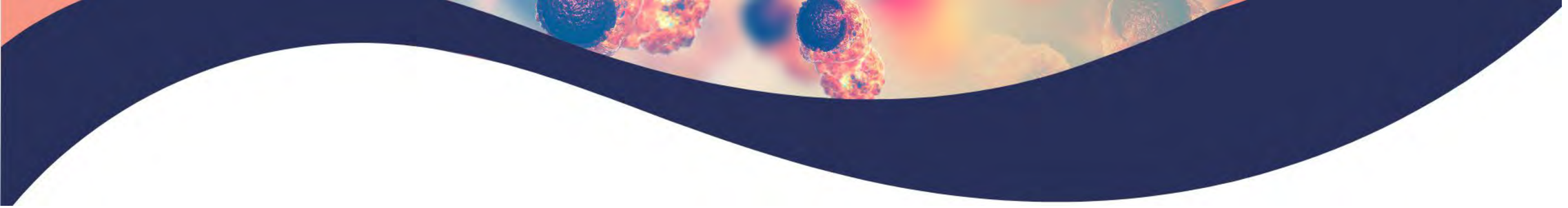

Front-Line Trials and Current Landscape

Amanda Nickles Fader, MD
Johns Hopkins University
Baltimore, Maryland, USA

2024 SGO Winter Meeting

January 25, 2024

GOG FOUNDATION®
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The Challenge of Treating Advanced/Recurrent Endometrial Cancer

- Despite frequent initial-or subsequent—treatment responses, prolonged remission or curative intent remain elusive for most patients with metastatic solid tumors
- **Greatest contributor to cancer mortality: treatment-resistant, metastatic disease**
- 5-year survival for patients with advanced/recurrent endometrial cancer disease 15-20%
  - oCarboplatin/paclitaxel (C/P): standard of care
  - oC/P alone in GOG/NRG Oncology trials: Median PFS rates of patients with biomarker unselected or mismatch repair proficient tumors ~8-13 months
  - o High-grade or measurable disease, tumors with rare histologies, non-Hispanic Black women
- **The reality: cytotoxic chemotherapy is only moderately effective in EC**
- **Tumoral molecular/mutational profile is key**

rapid communication

Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209)

David S. Miller, MD[1]; Virginia L. Filiaci, PhD[2]; Robert S. Mannel, MD[3]; David E. Cohn, MD[4]; Takashi Matsumoto, MD[5]; Krishnansu S. Tewari, MD[6]; Paul DiSilvestro, MD[7]; Michael L. Pearl, MD[8]; Peter A. Argenta, MD[9]; Matthew A. Powell, MD[10]; Susan L. Zweizig, MD[11]; David P. Warshal, MD[12]; Parviz Hanjani, MD[13]; Michael E. Carney, MD[14]; Helen Huang, MS[2]; David Cella, PhD[15]; Richard Zaino, MD[16]; and Gini F. Fleming, MD[17]

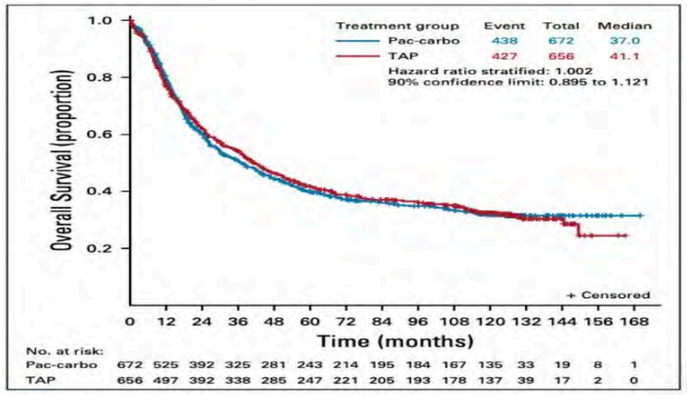

FIG 3. Updated overall survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

Miller J Clin Oncol, 2012, Powell, J Clin Oncol 2022,

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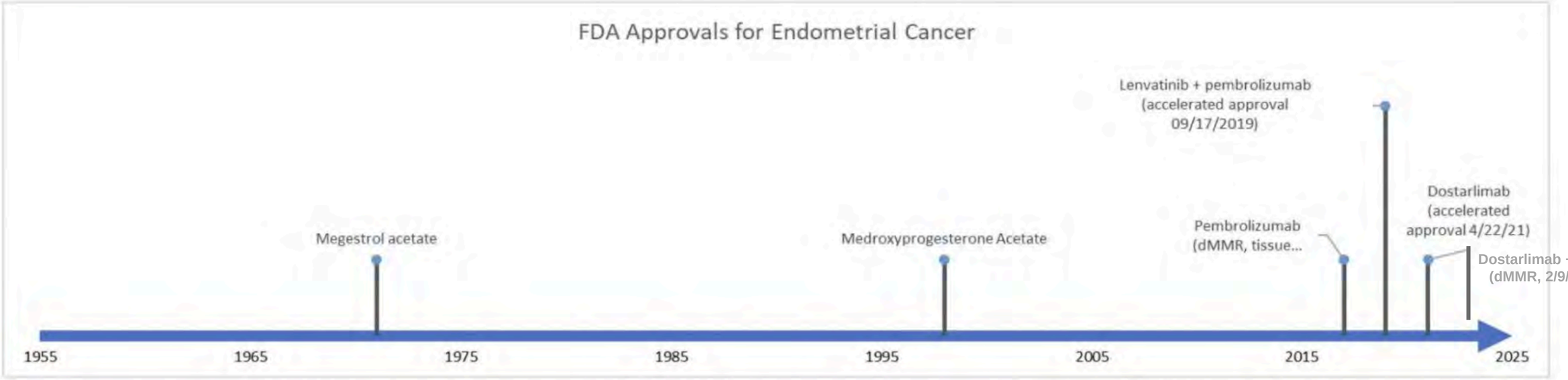
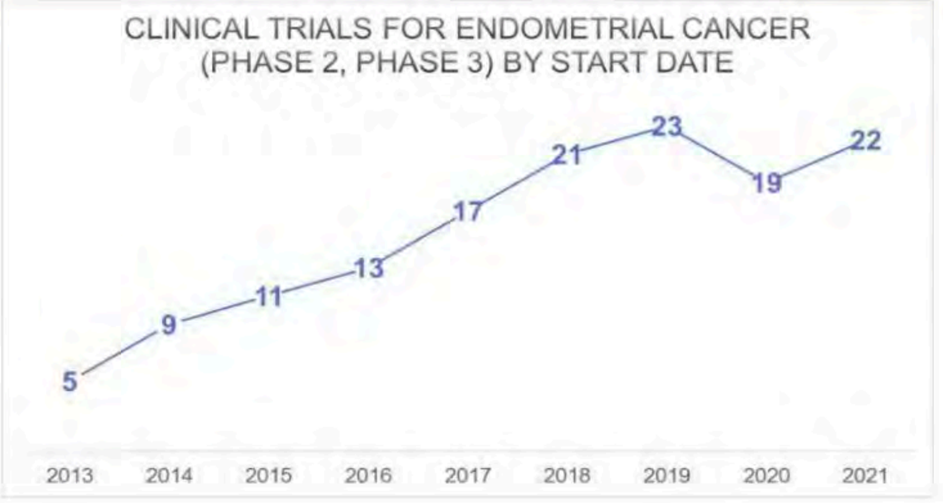
New Developments in Endometrial Cancer





Courtesy of Stephanie Gaillard, MD, PhD

JOHNS HOPKINS MEDICINE

A Decade of Practice-Changing Advancements in the Treatment of Advanced-Stage Endometrial Carcinoma

rapid communications

Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209)

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ORIGINAL ARTICLE

Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer

Daniela Matei, M.D., Virginia Filiaci, Ph.D., Marcus E. Randall, M.D., David Mutch, M.D., Margaret M. Steinhoff, M.D., Paul A. DiSilvestro, M.D., Katherine M. Moxley, M.D., Yong M. Kim, M.D., Ph.D., Matthew A. Powell, M.D., David M. O'Malley, M.D., Nick M. Spirtos, M.D., William Small, Jr., M.D., et al.

original reports

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

Matthew A. Powell, MD[1]; Virginia L. Filiaci, PhD[2]; Martee L. Hensley, MD[3]; Helen Q. Huang, MS[2]; Kathleen N. Moore, MD[4]; Krishnansu S. Tewari, MD[5]; Larry J. Copeland, MD[6]; Angeles A. Secord, MD[7]; David G. Mutch, MD[8]; Alessandro Santin, MD[9]; David P. Warshal, MD[10]; Nick M. Spirtos, MD[11]; Paul A. DiSilvestro, MD[12]; Olga B. Ioffe, MD[13]; and David S. Miller, MD[14]

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mansoor R. Mirza, M.D., Dana M. Chase, M.D., Brian M. Slomovitz, M.D., René dePont Christensen, Ph.D., Zoltán Novák, Ph.D., Destin Black, M.D., Lucy Gilbert, M.D., Sudarshan Sharma, M.D., Giorgio Valabrega, M.D., Lisa M. Landrum, M.D., Ph.D., Lars C. Hanker, M.D., Ashley Stuckey, M.D., et al., for the RUBY Investigators*

Carboplatin and paclitaxel plus avelumab compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial

Sandro Pignata, MD • Prof Giovanni Scambia, MD • Clorinda Schettino, MD • Laura Arenare, MSc • Carmela Pisano, MD • Davide Lombardi, MD • et al. Show all authors • Show footnotes

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., et al.

Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

Authors: Shannon N. Westin, MD, MPH | Kathleen Moore, MD, Hye Sook Chon, MD, Jung-Yun Lee, MD | Jessica Thomes Pepin, MD, Michael Sundborg, MD, Ayelet Shai, MD, PhD, ... SHOW ALL ... on behalf of the DUO-E Investigators AUTHORS INFO & AFFILIATIONS

Journal of Clinical Oncology > List of Issues > Volume 40, Issue 9 >

ORIGINAL REPORTS | Gynecologic Cancer

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

Check for updates

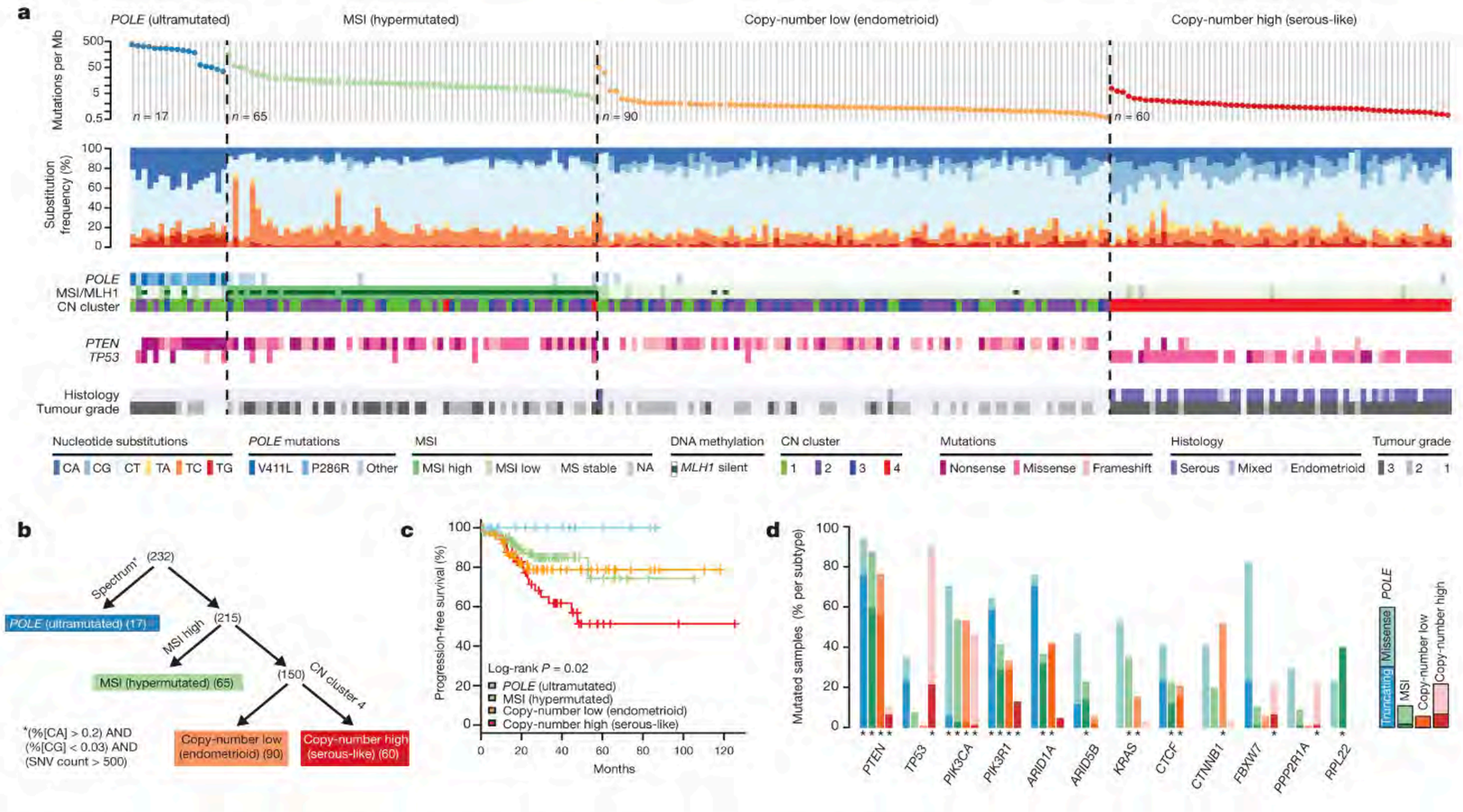
Matthew A. Powell, MD[1]; Virginia L. Filiaci, PhD[2]; Martee L. Hensley, MD[3]; Helen Q. Huang, MS[2]; Kathleen N. Moore, MD[4]; Krishnansu S. Tewari, MD[5]; Larry J. Copeland, MD[6]; Angeles A. Secord, MD[7]; David G. Mutch, MD[8]; Alessandro Santin, MD[9]; David P. Warshal, MD[10]; Nick M. Spirtos, MD[11]; Paul A. DiSilvestro, MD[12]; Olga B. Ioffe, MD[13]; and David S. Miller, MD[14]

Published in final edited form as:
Clin Cancer Res. 2020 August 01; 26(15): 3928–3935. doi:10.1158/1078-0432.CCR-20-0953.

Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis

Amanda N. Fader[1], Dana M. Roque[2], Eric Siegel[3], Natalia Buza[4], Pei Hui[4], Osama Abdelghany[4], Setsuko Chambers[5], Angeles Alvarez Secord[6], Laura Havrilesky[6], David M. O'Malley[7], Floor J. Backes[7], Nicole Nevadunsky[8], Babak Edraki[9], Dirk Pikaart[10], William Lowery[11], Karim ElSahwi[12], Paul Celano[13], Stefania Bellone[4], Masoud Azodi[4], Babak Litkouhi[14], Elena Ratner[4], Dan-Arin Silasi[4], Peter E. Schwartz[4], Alessandro D Santin[4,*]

Mutation Spectra Across Endometrial Carcinomas



- Mismatch repair proficient (pMMR)HER2 and/or p53 overexpressed/mutated tumors have the worst prognosis
- We must focus our efforts on drug development and novel synergistic combination strategies in this patient population

G Getz *et al. Nature* **497**, 67-73 (2013)
doi:10.1038/nature12113

nature

displayed.

GOG FOUNDATION

World Health Organization

NCCN National Comprehensive Cancer Network®

ESGO/ESTRO/ESP

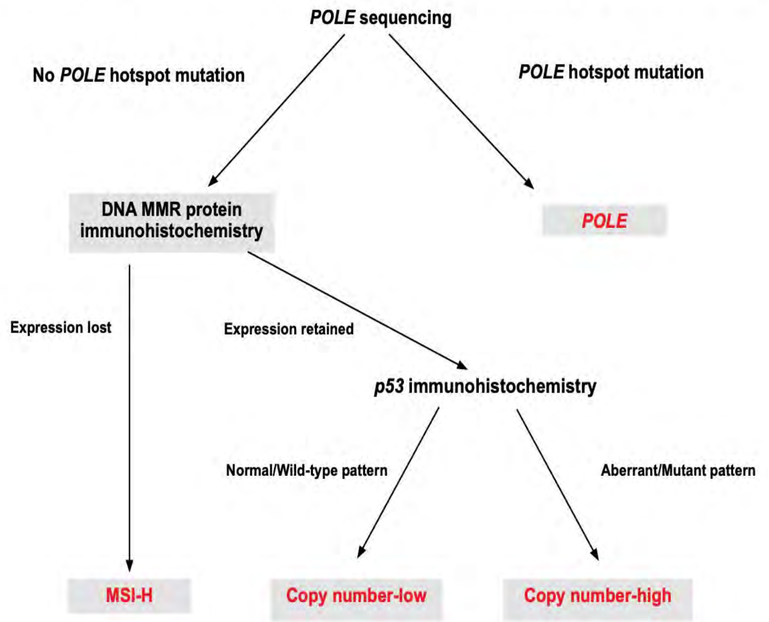
NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

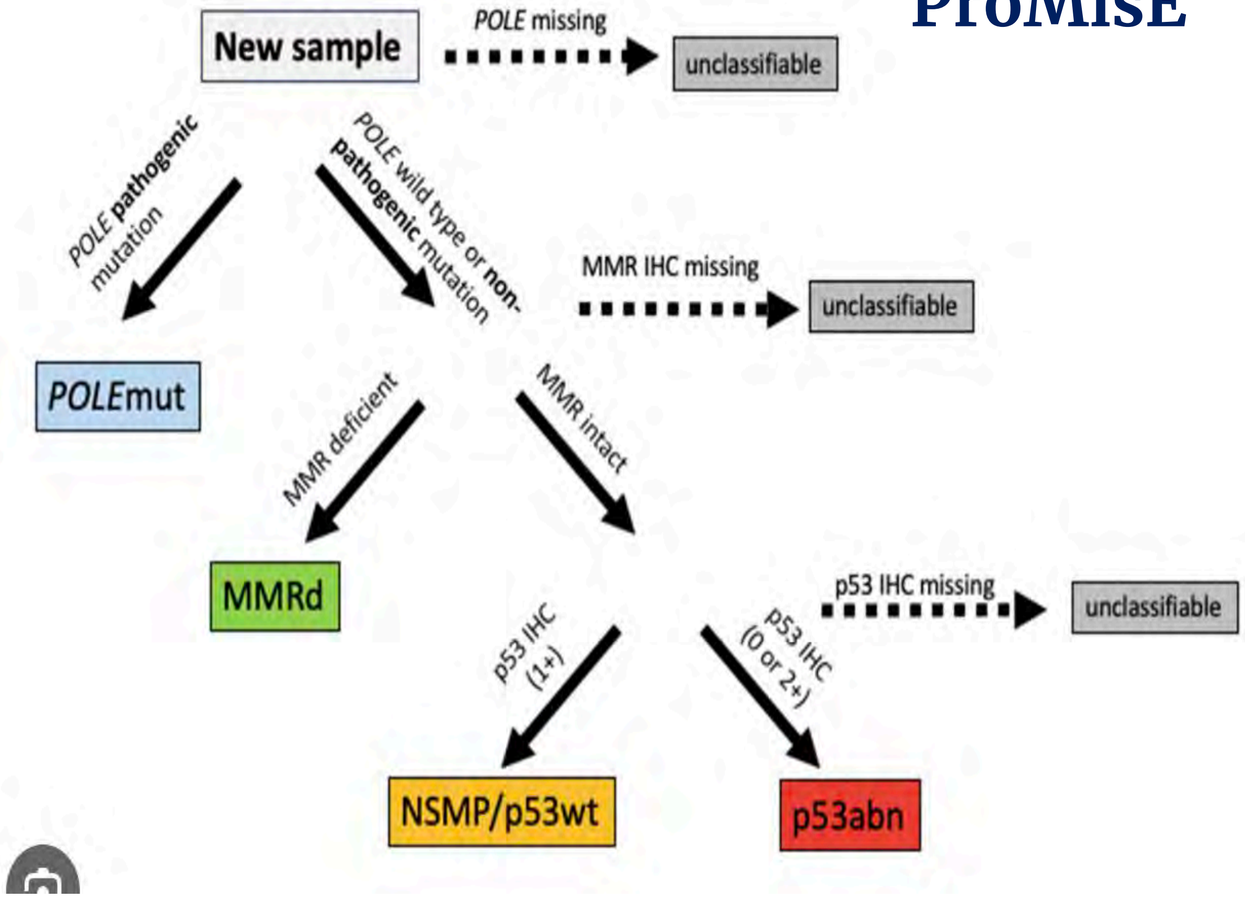
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)[f,g]



[f] Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.

ProMisE



Kommoss et al, Annals Oncol, 2018

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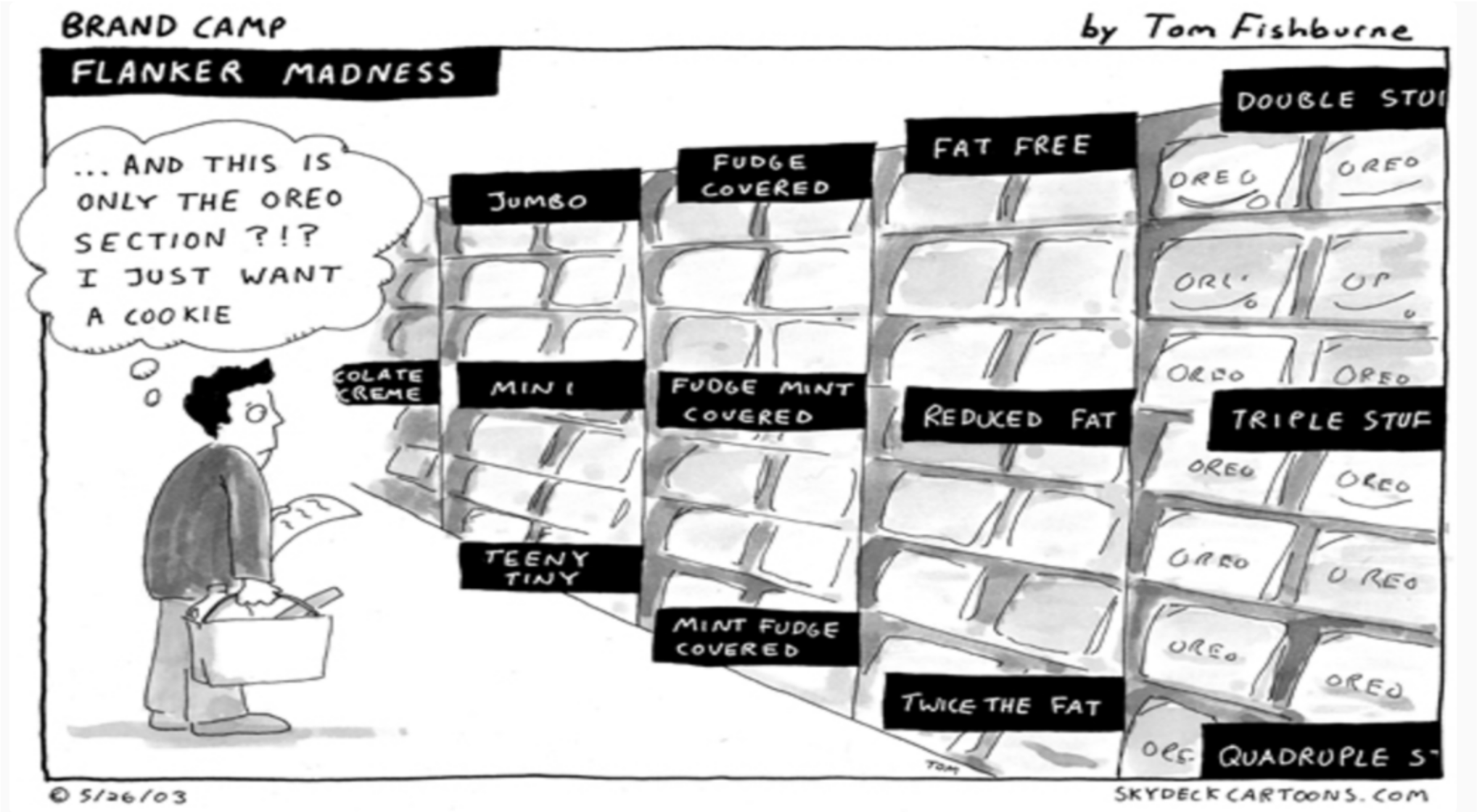
Talk Objectives



- **Choice Overload!**
- **The paradox of choice**

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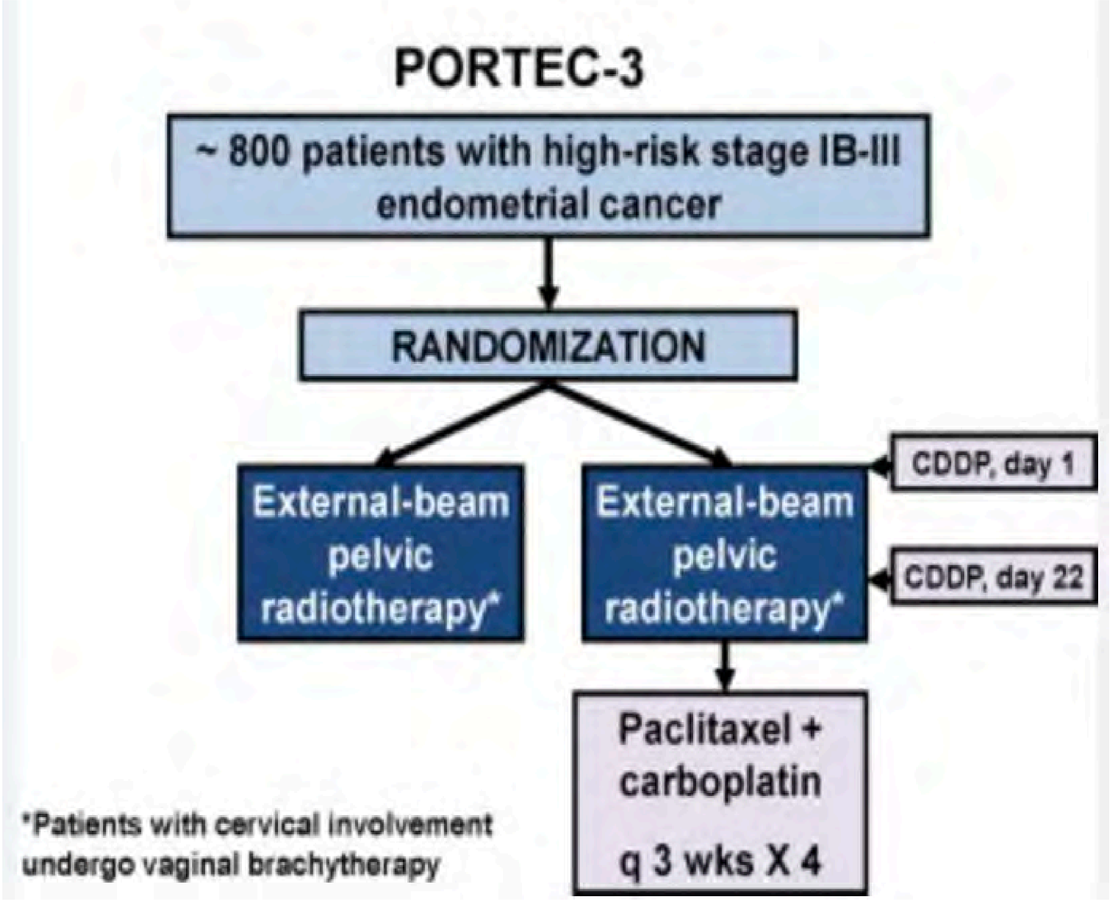
PORTEC-3 Study Design

Key eligibility criteria:

- Newly diagnosed endometrial carcinoma s/p TAH/BSO +/- LND
- Stage I, endometrioid grade 3 with deep myometrial invasion or LVSI (or both)
- Endometrioid stage II or III
- Stage I-III with serous or clear cell histology (IA with +MI)
- No residual disease



De Boer et al, Lancet Oncol, 2019

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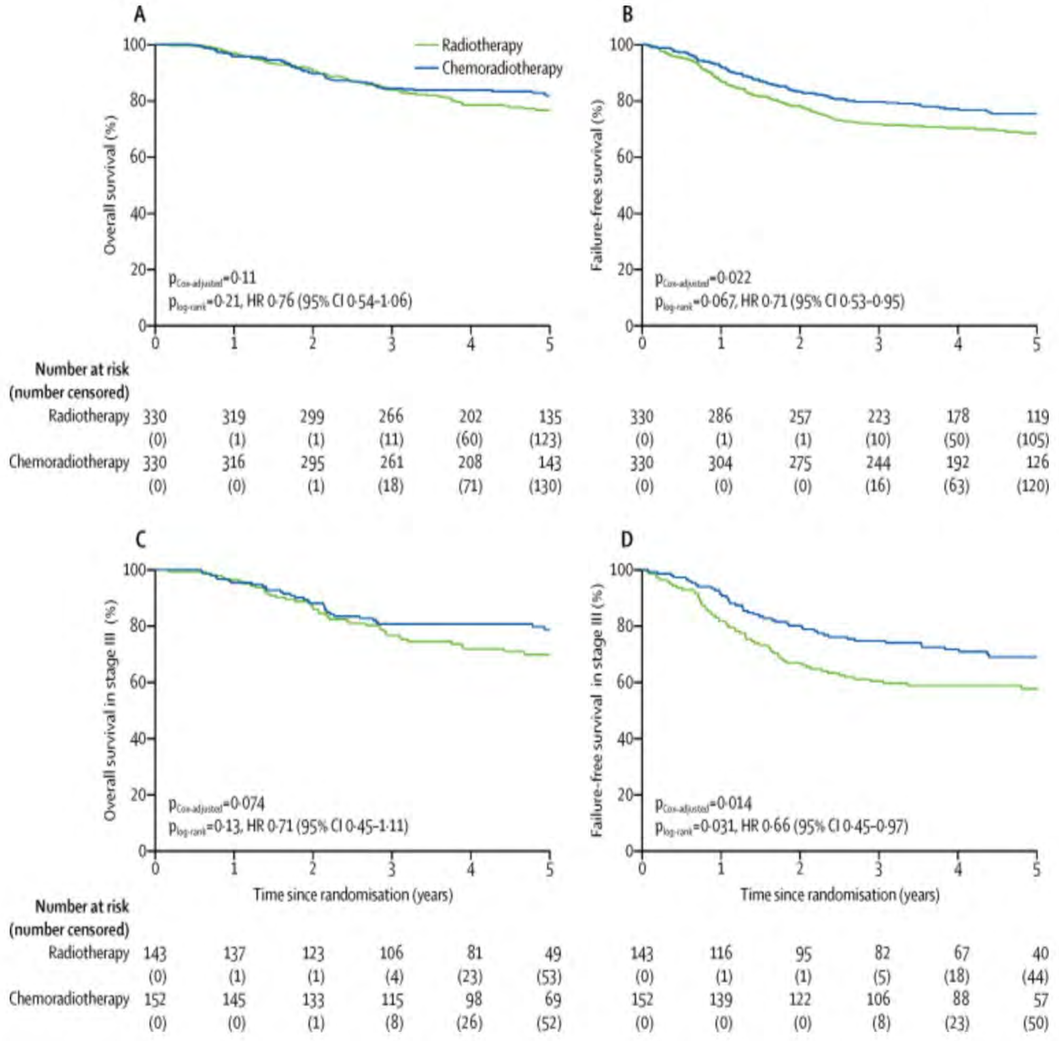
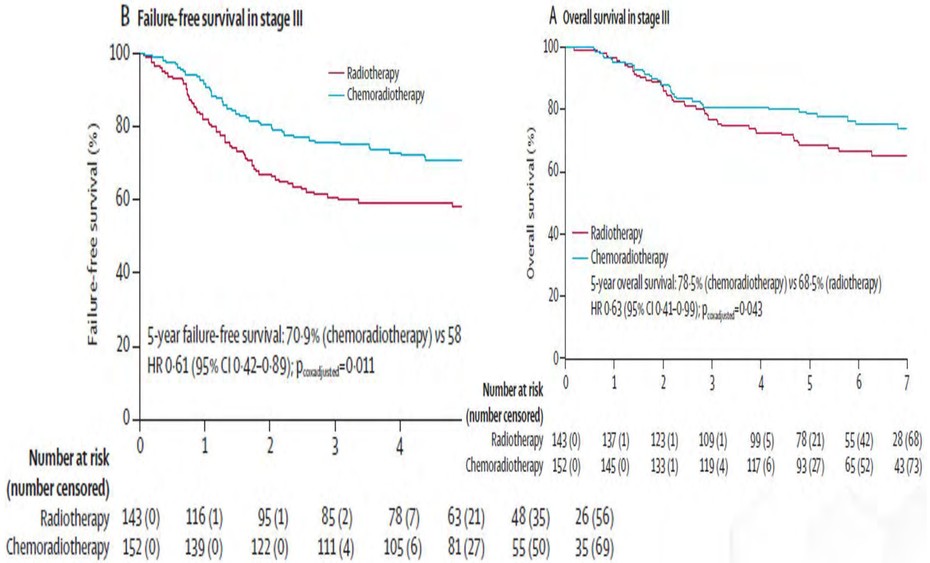
PORTEC-3 Results



Overall survival and failure-free survival



Serous carcinoma (stage I-III)

- 5-year failure-free survival: 59·7% (chemoRT) *vs* 47·9% (RT)
  HR 0·42 (95% CI 0·22–0·80)
- 5-year overall survival: 71·4% (chemoRT) *vs* 52·8% (RT)
  HR 0·48 (95% CI 0·24–0·96)

de Boer SM, et al. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30395-X/fulltext.

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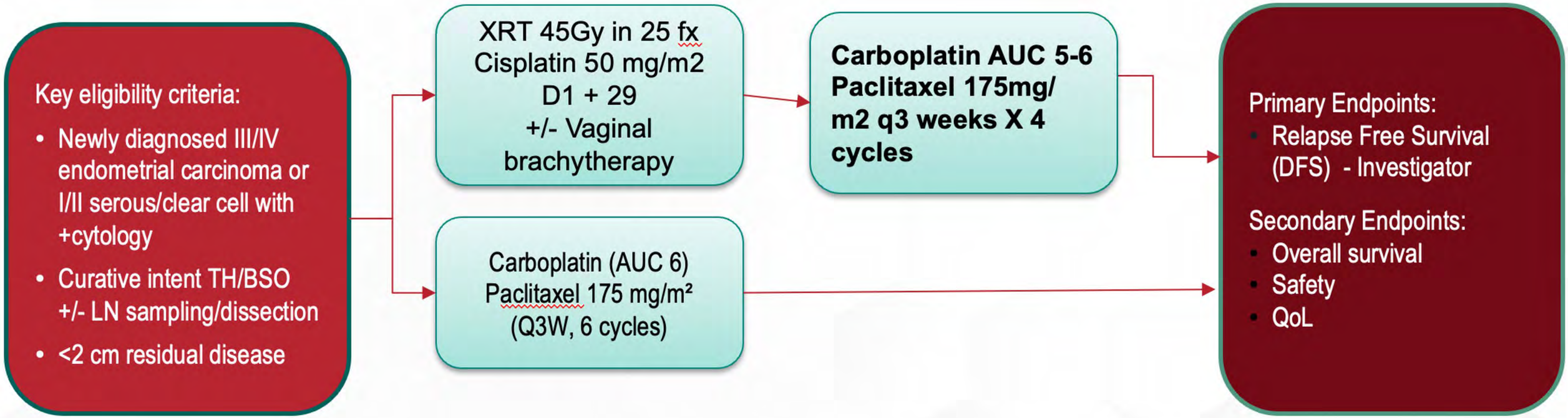
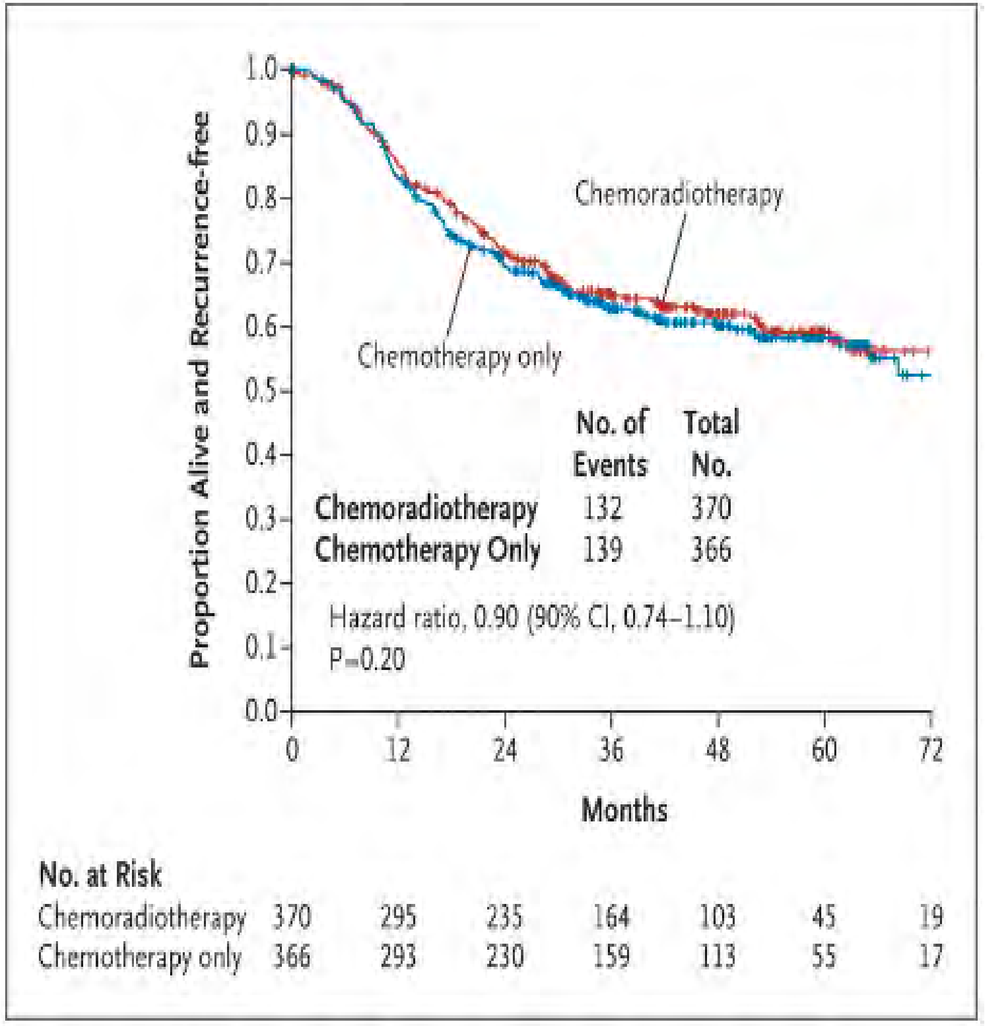
GOG 258 Study Design

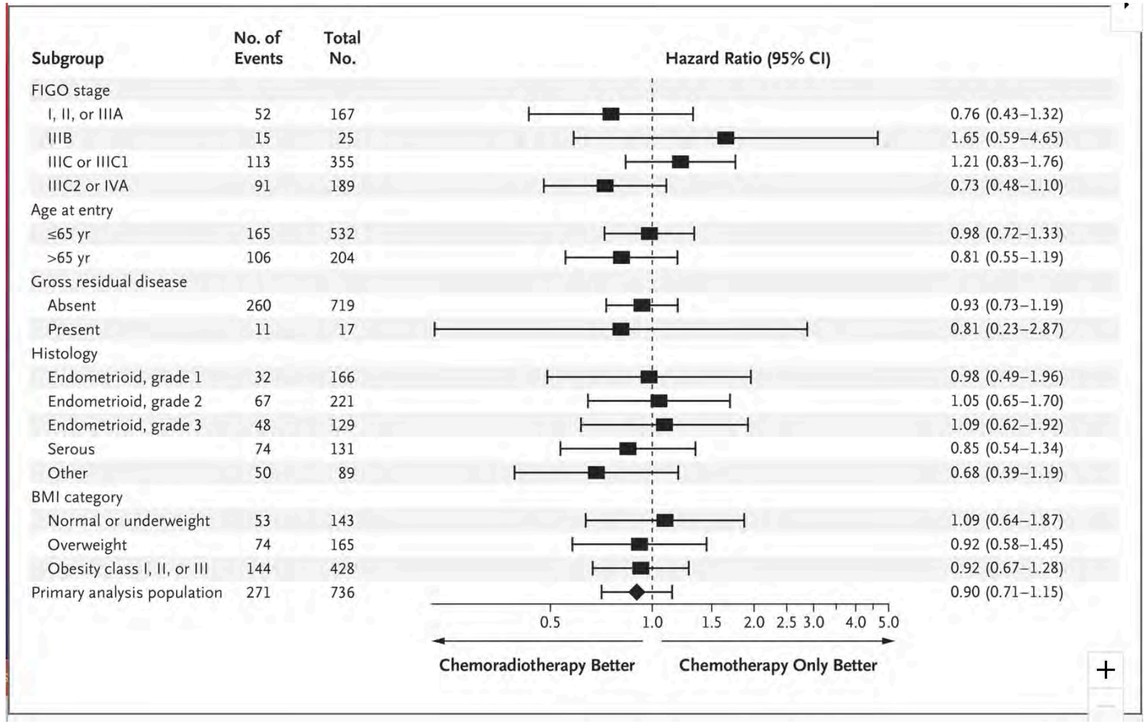


Matei D, et al. *N Engl J Med*. 2019;380(24):2317-2326.

GOG 258



Conclusions: PROs indicate that the chemoradiotherapy group experienced worse HRQoL and GI toxicity compared to patients randomized to chemotherapy alone for locally advanced endometrial cancer though based on the MID, these were not clinically meaningful differences. The GI symptom subscale was a reliable and valid scale that has value for future trials.



SGO 2023 Annual Meeting: Recurrence-free survival was not improved with the combination over chemotherapy alone. After a median follow-up of 112 months, **the HR for overall survival with chemoradiotherapy (CRT) was 1.05. Local recurrences better with CRT, but increased distant recurrences**

Matei, N Engl J Med 2019; 380:2317-2326

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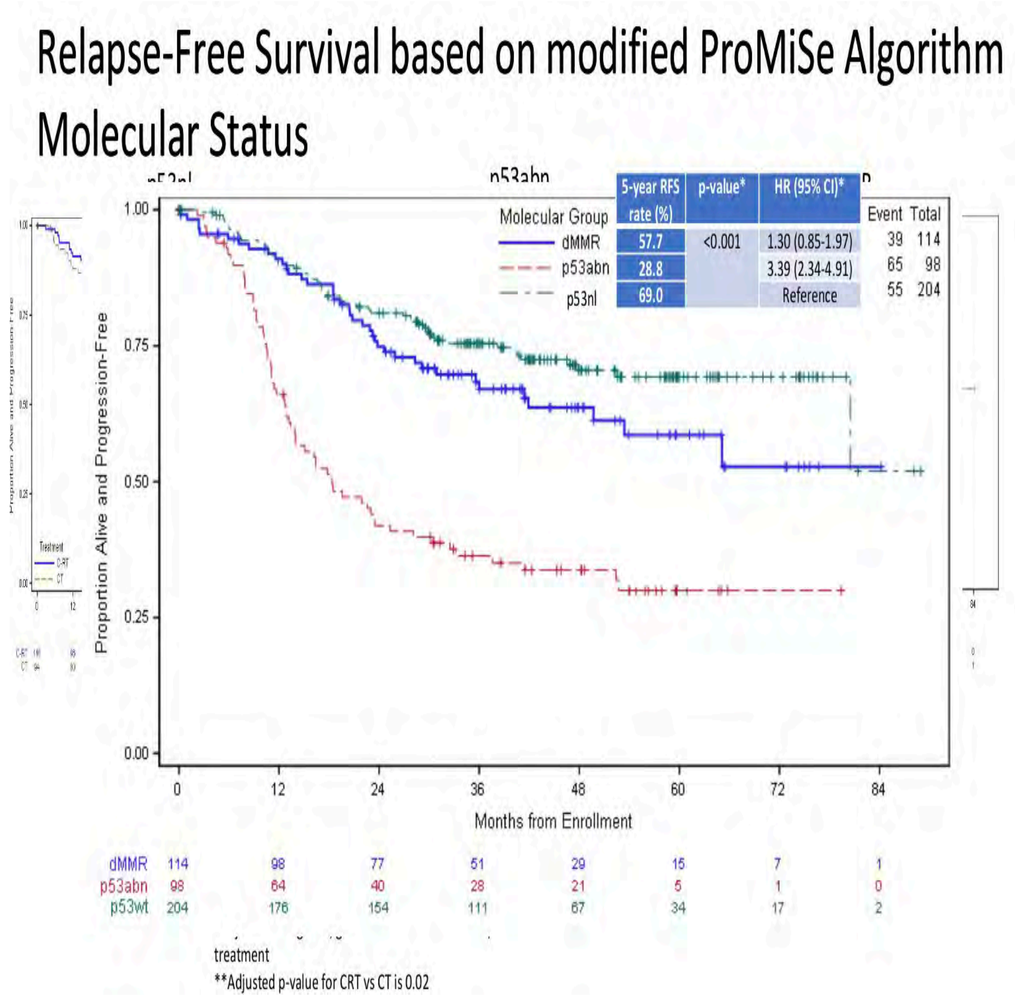
PORTEC-3 and GOG 258 molecular analyses

TCGA group	n	Treatment	5-yr RFS	HR (95% CI)	5-year OS	HR (95% CI)
p53abn	93 (23%)	EBRT versus CisRT + chemo	36.2% 58.6%	1 0.52 (0.30-0.91)	41.8% 64.9%	1 0.55 (0.30-1.00)
POLEmut	51 (12%)	EBRT versus CisRT + chemo	96.6% 100%	1 0.02 (<0.01->10^5)	96.6% 100%	1 0.02 (<0.01->10^5)
MMRd	137 (33%)	EBRT versus CisRT + chemo	75.5% 68%	1 1.29 (0.68-2.45)	84% 78.6%	1 1.33 (0.64-2.75)
NSMP	129 (32%)	EBRT versus CisRT + chemo	67.7% 79.7%	1 0.68 (0.36-1.3)	87.6% 89.3%	1 0.68 (0.26-1.77)

TCGA = The Cancer Genome Atlas; NSMP = no specific molecular profile; EBRT = external beam radiation; CisRT = cisplatin/radiotherapy. Leon-Castillo, 2020.



Clements et al, IGCS 2023

GOG FOUNDATION

- Phase II Randomized
- 1º End-Point: PFS
- N= 349

GOG#0086P

- Eligibility:
- Stage III or IVA EC measurable disease
- Stage IVB or Recurrent EC (whether there is measurable disease or not)
- No prior Chemotherapy

Arm 1:
Paclitaxel 175 mg/m2 IV over 3 hours day 1
Carboplatin AUC = 6 IV day 1
Bevacizumab 15mg/kg IV day 1
Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

Arm 2:
Paclitaxel 175 mg/m2 IV over 3 hours day 1
Carboplatin AUC = 5 IV day 1
Temsirolimus 25 mg IV days 1 and 8
Maintenance regimen – Temsirolimus 25 mg IV weekly. Days 1,8 and 15 until disease progression or prohibition of further therapy.

Arm 3:
Ixabepilone 30 mg/m2 IV over 1 hour day 1
Carboplatin AUC = 6 IV day 1
Bevacizumab 15mg/kg IV day
Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

PI: Carol Aghajanian, M.D.
From: 9/14/2009 to 9/9/2014
ClinicalTrials.gov Identifier:NCT00977574

GOG FOUNDATION

GOG 0086-P: p53

Courtesy of Dr. Kimberly Leslie

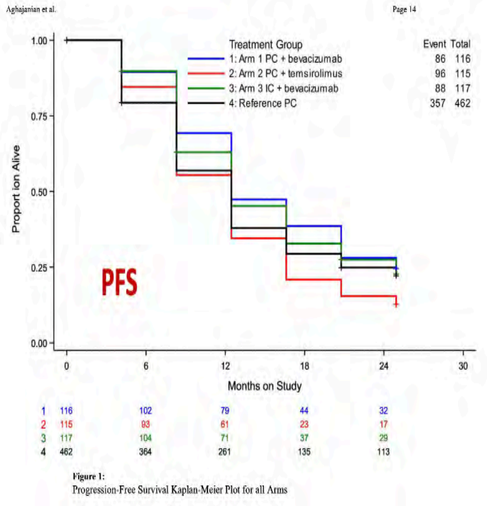


Figure 1:
Progression-Free Survival Kaplan-Meier Plot for all Arms

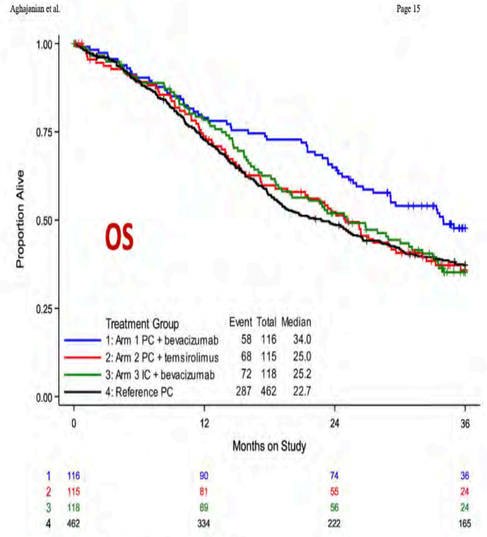
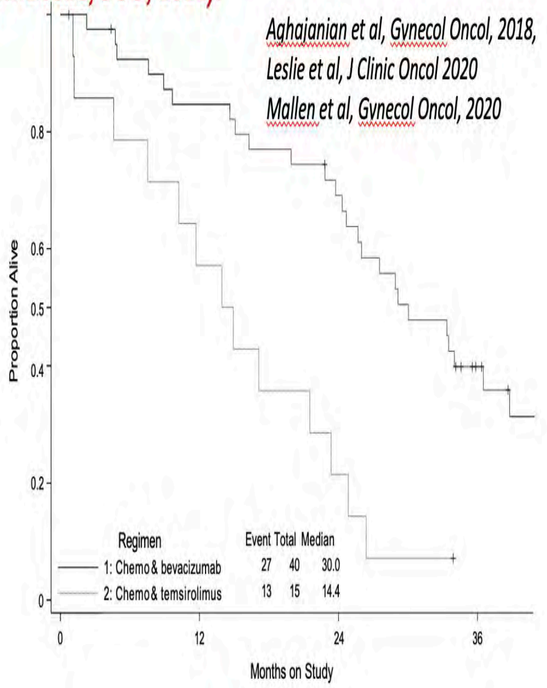


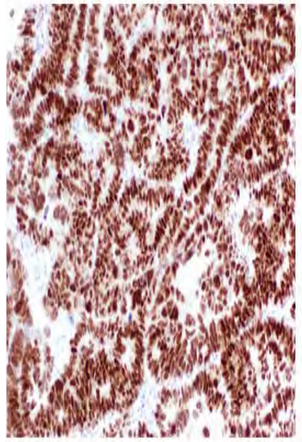
Figure 2:
Overall Survival Kaplan-Meier Plot for all Arms

From GOG Study 86P Survival by Treatment Group Integrated for Missense TP53 and IHC p53 Over-Expressed (IHC for p53 may serve as a predictive biomarker for bevacizumab upfront + chemotherapy, Thiel…Leslie, JCO, 2022).

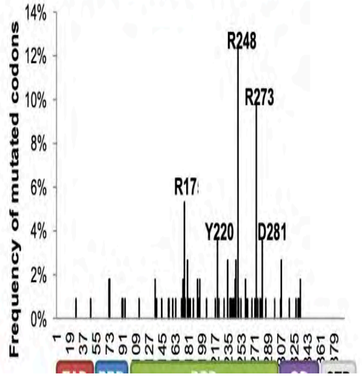


55 of 213 (26%) of the patients on GOG 86P met the criteria to be classified within this group.

p53 Over-Expressed (OE) staining by IHC



***TP53* missense mutation by sequencing**



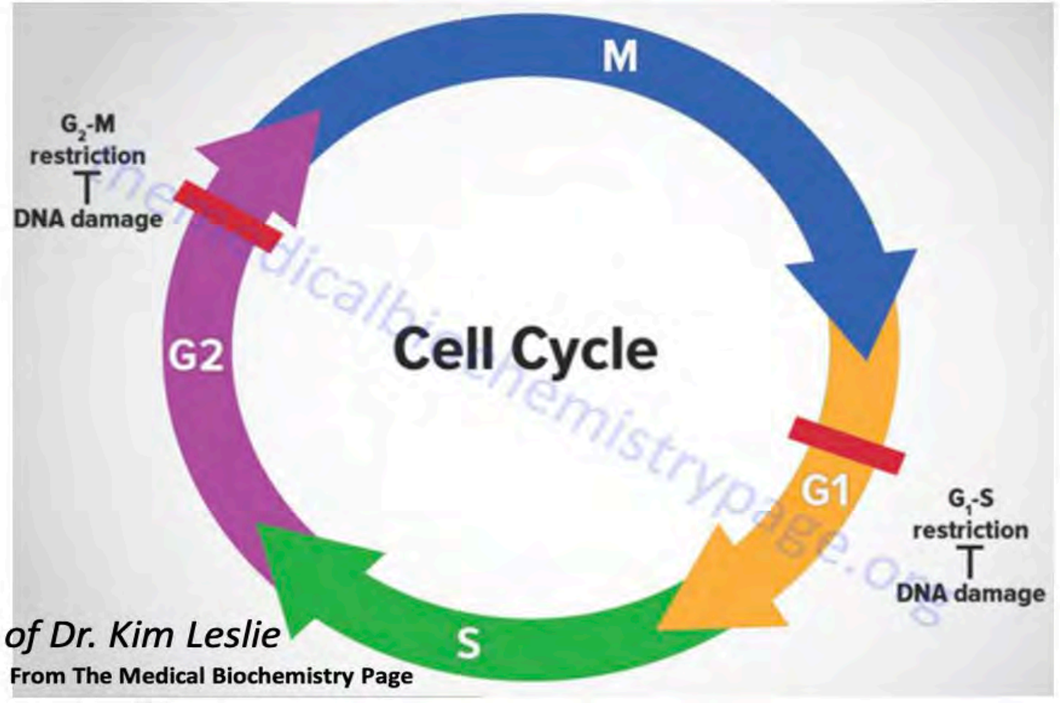
Median Overall Survival 30.0 months on bevacizumab + chemo versus 14.4 months for temsirolimus + chemo, a significant improvement in outcomes for a high risk patient group with generally poor OS with standard therapy.

OS Hazard Ratio 0.28 [0.14-0.59] when bevacizumab is given upfront with chemotherapy.

Courtesy of Dr. Kimberly Leslie

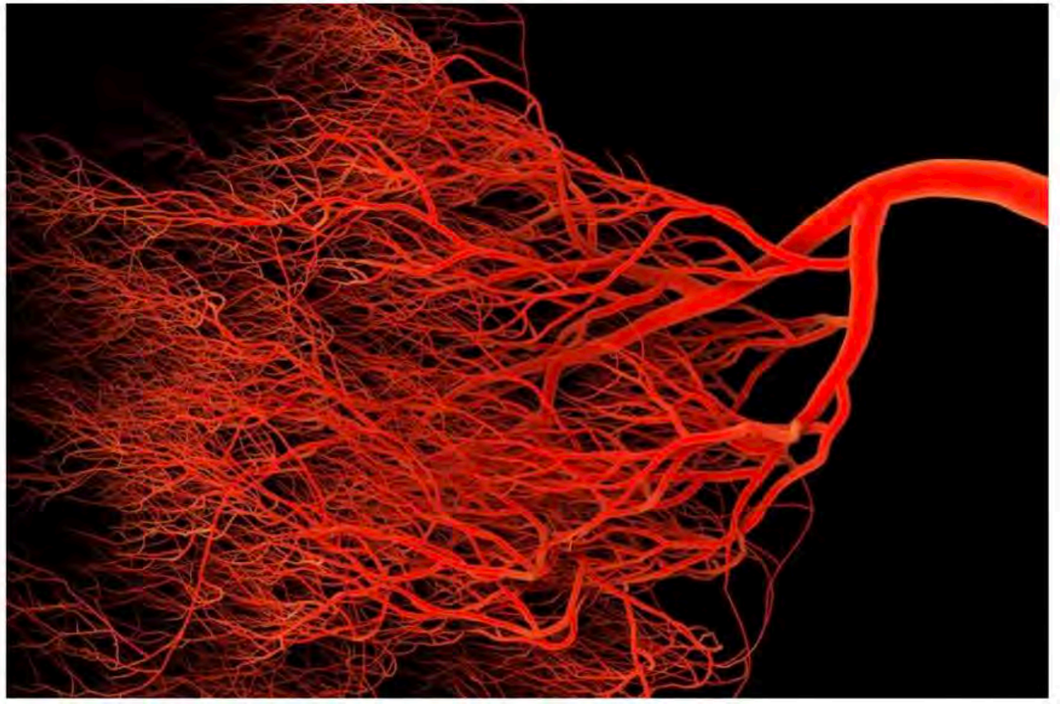
Why are mutations in p53 potentially relevant to bevacizumab + chemotherapy sensitivity?

- **Cell cycle checkpoint abrogation**: Cells with mutated p53 lack the normal cell cycle checkpoints, preventing DNA repair. This makes cancer cells ***more vulnerable to chemotherapy***.



Courtesy of Dr. Kim Leslie
From The Medical Biochemistry Page

- **Angiogenesis**: Mutated p53 enhances VEGF expression and tumor angiogenesis, making cells ***more vulnerable to antiangiogenics***.



P53 wild type maintenance therapy

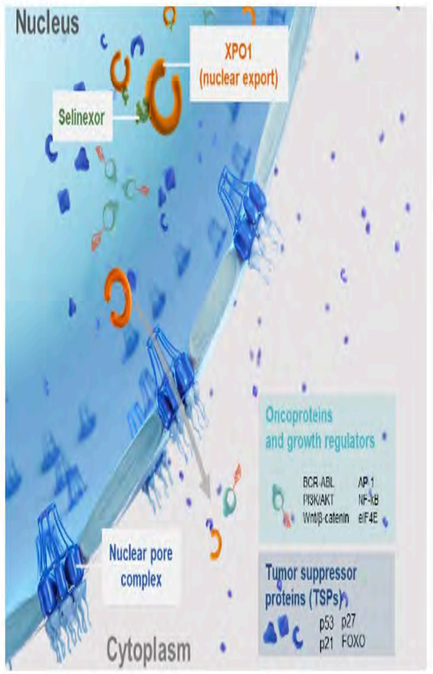
GOG-3055/ENGOT-EN5/SIENDO (NCT03555422)

- Selinexor, a first-in-class oral selective inhibitor of the nuclear export compound that selectively binds to nuclear protein exportin 1 and inhibits its export, and blocks the nuclear export of tumor suppressor, growth regulatory, and anti-inflammatory proteins
- Phase 3, multicenter, double-blind, placebo-controlled, randomized study; **maintenance after chemotherapy** (stage IV or recurrent endometrial cancer); N=263
- Selinexor 80 or 60 mg on days 1, 8, 15, and 22 of each 28-day cycle
- Primary endpoint: median PFS 5.7 vs 3.8 months; HR 0.70 (p=0.0486)
- In pre-specified subgroup of p53wt: median PFS 13.7 vs 3.7 months; HR 0.38 (p=0.0006)

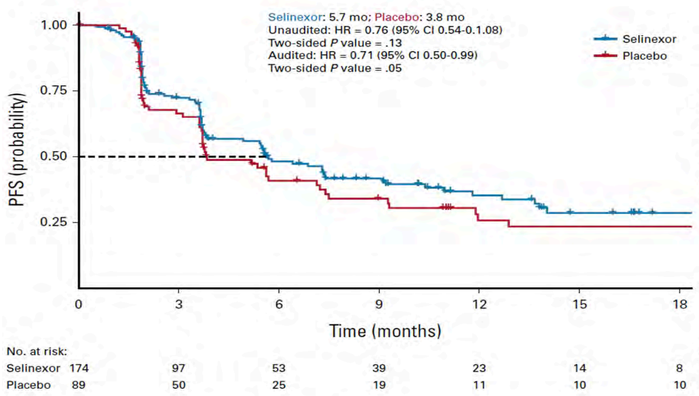
Vergote, JCO 2023

Selinexor

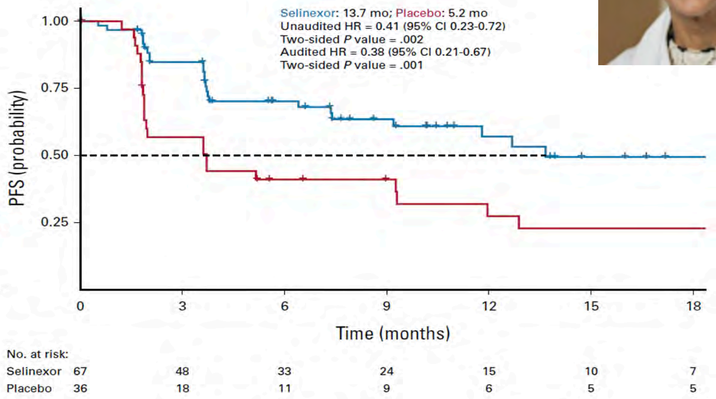
- XPO1 exports the major tumor suppressor proteins away from the nucleus
- Cancer cells
  - Overexpress XPO1
  - Inactivate cytoplasmic p53 through protein degradation
- Selinexor inhibits XPO1 nuclear export
  - Leads to retention and reactivation of TSPs in the nucleus and stabilization of p53
  - Results in selective killing of cancer cells



ENGOT-EN5/GOG-3055/SIENDO



Intention-to-treat population



patients with TP53 wild-type endometrial cancer

Vergote, JCO 2023

Makker et al, JCO, 2022

GOG FOUNDATION

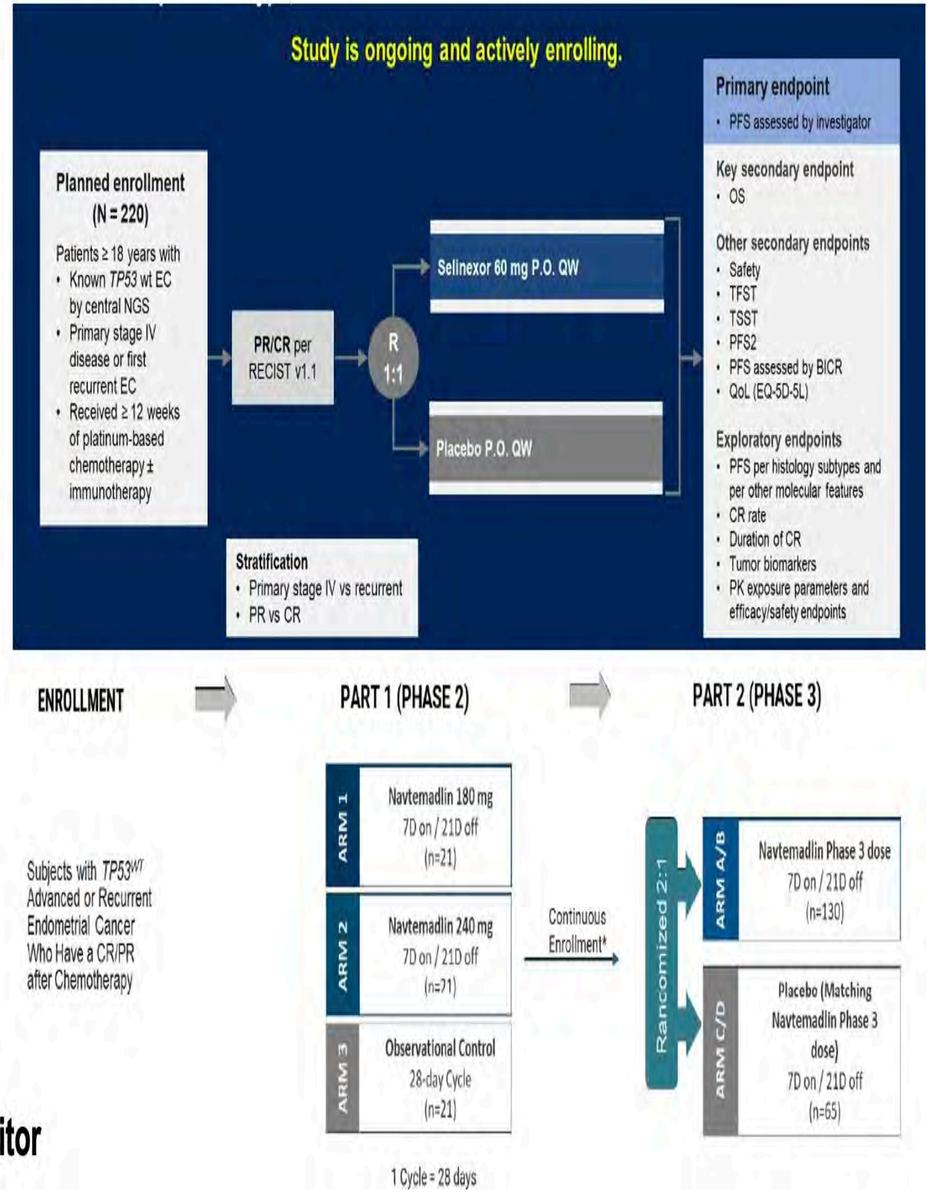
P53 restoration of p53 mediated apoptosis

ENGOT-EN20/GOG-3083
XPORT-EC-042
NCT05611931

Selinexor: XPO1 inhibitor

KRT-232-118/GOG-3089/
ENGOT en21
NCT05797831

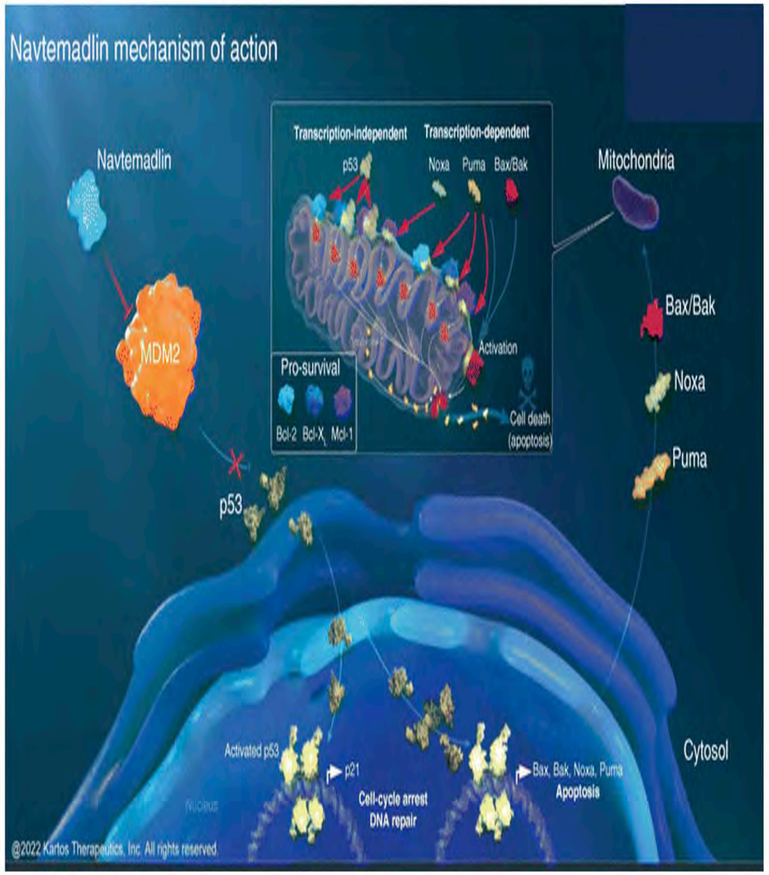
Navtemadlin: MDM2-inhibitor



KRT-232-11: Navtemadlin

Phase 2/3 Study of Navtemadlin as Maintenance Therapy in Subjects with TP53WT Advanced or Recurrent Endometrial Cancer Who Responded to Chemotherapy 8/GOG-3089

- Oral MDM2 inhibitor
- Restores p53 activity to drive apoptosis of wild type TP53 cells
- Expression of pro-apoptotic Bcl-2 family proteins



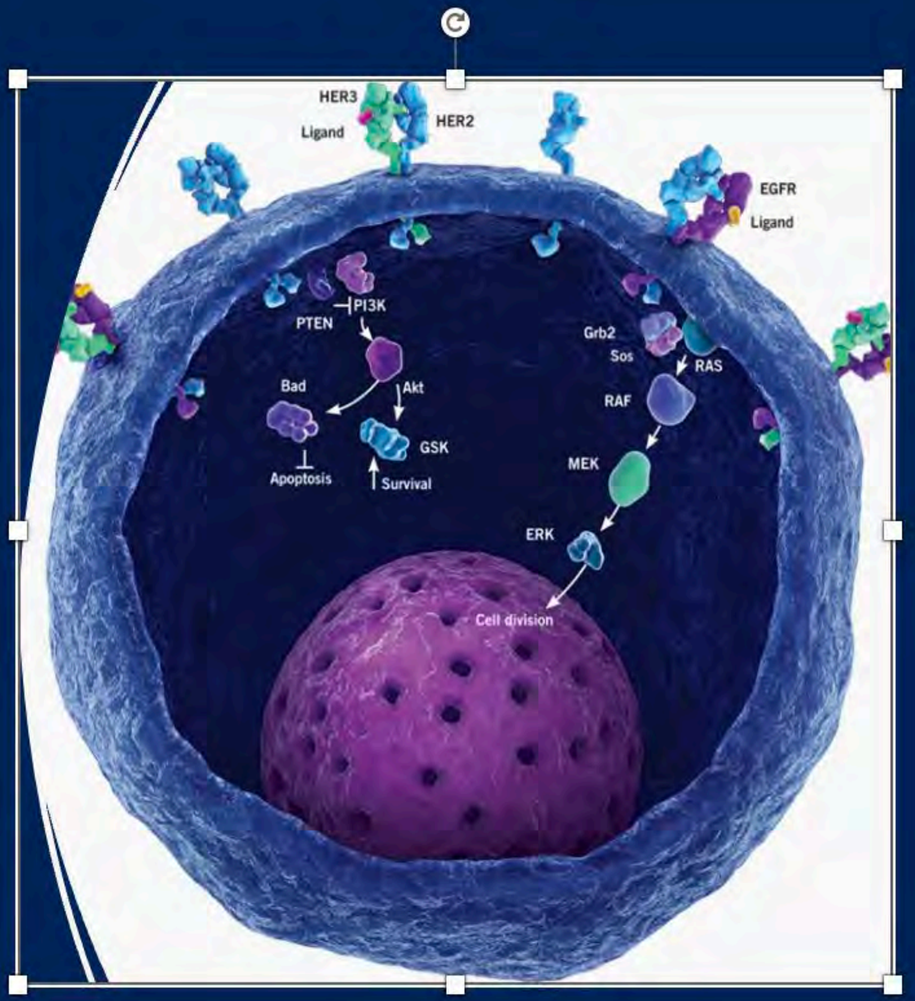
NCT05797831; Verstovsek S. BOREAS. Future Oncology 2022.

Treatment Based Upon Molecular Make Up: HER2

- *Her2/neu* overexpression by IHC demonstrated in 14-60% of USC. Estimates vary widely due to lack of standardized algorithms for interpretation and scoring of Her2 immunostains in endometrial cancer

- Dysregulation of *Her2/neu oncogene* reported in 27% of USC in Whole Exome Sequencing (WES) studies performed by TCGA network (Levine DA , Nature 2013)

- HER2/neu functions as preferred partner for heterodimerisation with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and responsible for regulating cell growth and differentiation

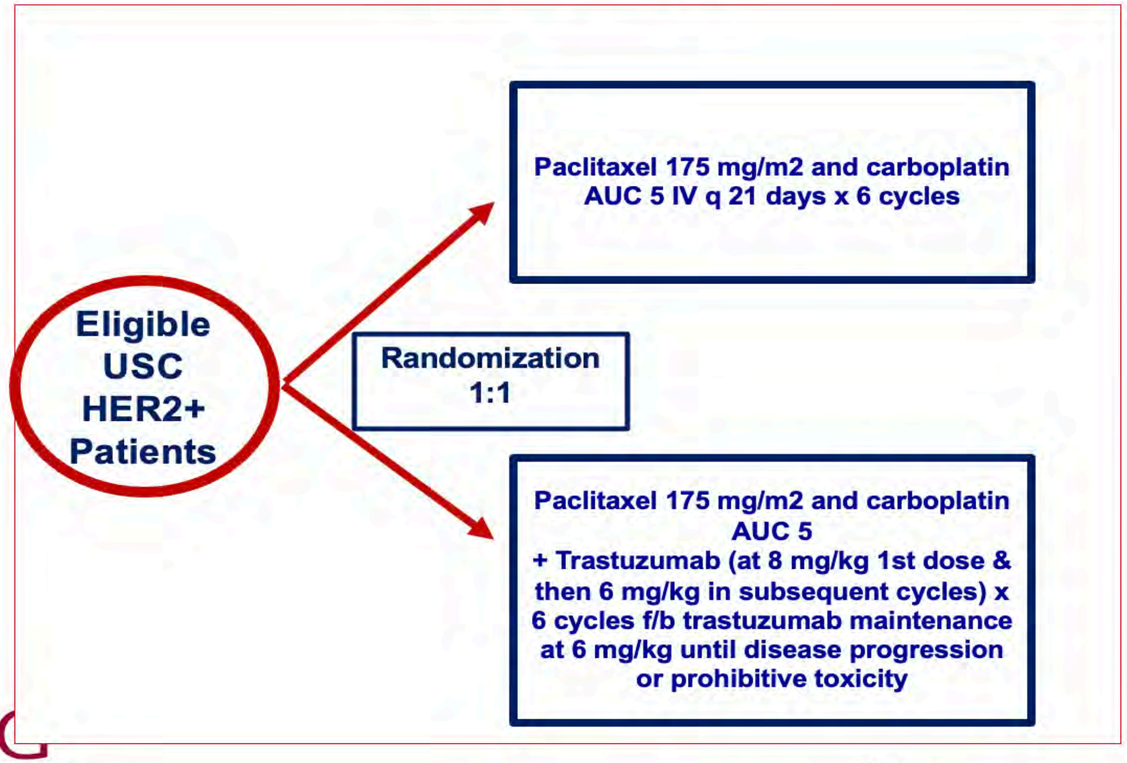


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

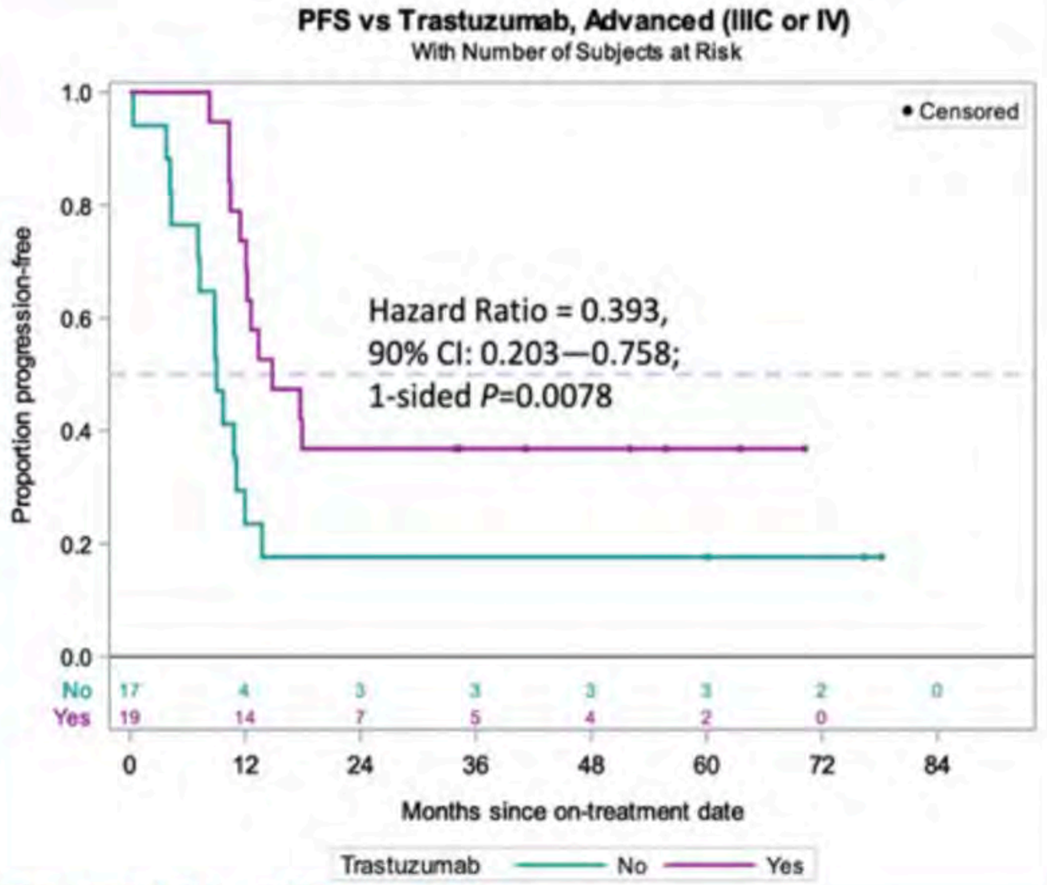
Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

Study Design

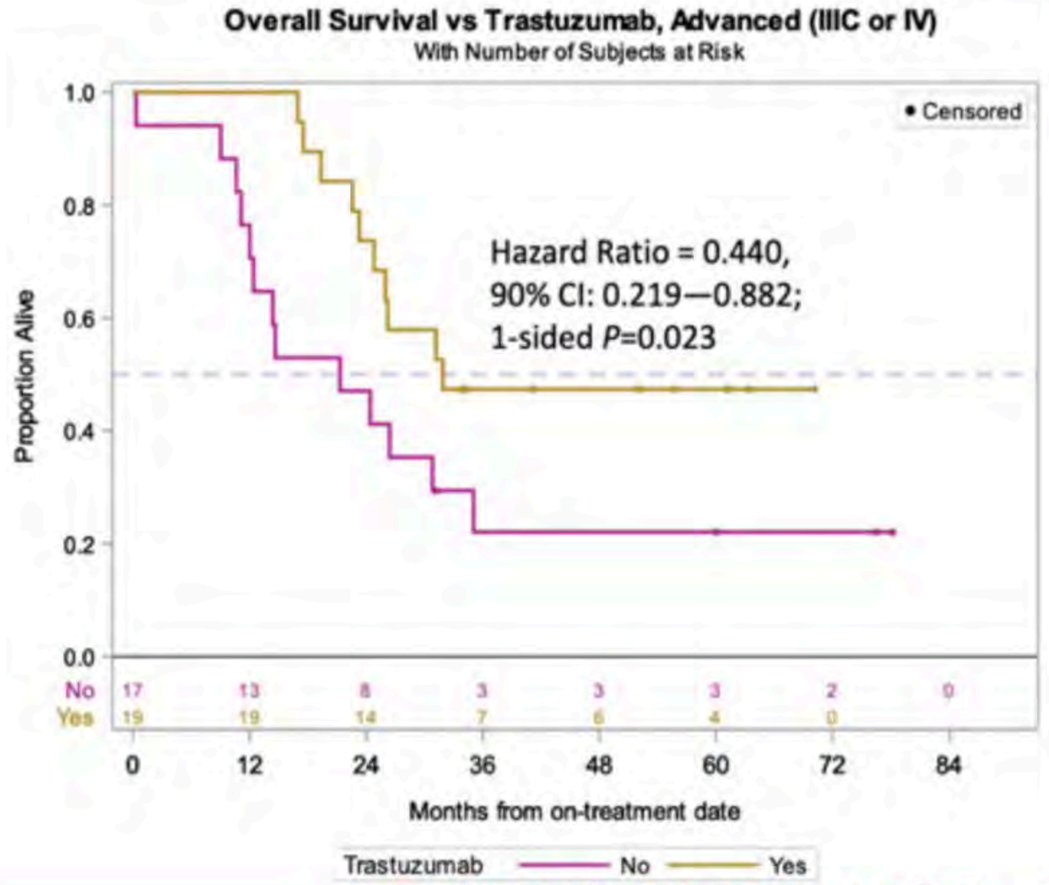


- 61 patients with advanced stage/recurrent HER2+ USC
- 3+ IHC, or 2+ with FISH + (modified 2007 ASCO/CAP)
- Measurable/non-measurable disease

Improvement in PFS and OS for Advanced-Stage Disease with Addition of Trastuzumab



Fader AN, JCO, 2018



Fader AN, Clin Cancer Res, 2020

NRG GY-026

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
TransIx PI: Alessandro Santin

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Arm 1:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/ prohibitive toxicity)

Safety Lead-In (n=45)

Arm 3:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

Strata:
- Stage (I-II vs III-IV)
- Measurable vs. non-measurable dz
- Histology (serous vs carcinosarcoma)

Immune Checkpoint Inhibitor Therapy in Endometrial Cancer

Pembrolizumab (KN-158): Robust Antitumor Activity in Patients With MSI-H Advanced EC

Variable	MSI-H EC n = 79	EC (biomarker unselected) n = 107
ORR % (95% CI)	**48** (37-60)	**11.2** (5.9-18.8)
Complete response	11 (14)	0
Partial response	27 (34)	12 (11.2)
Stable disease	14 (18)	26 (24.3)
Progressive disease	23 (29)	56 (52.3)
Not evaluable	1 (1)	2 (1.9)
Not assessed	3 (4)	11 (10.3)

Dostarlimab (GARNET Cohorts A1 & A2): Clinical Benefit in dMMR and MMRp EC Patients

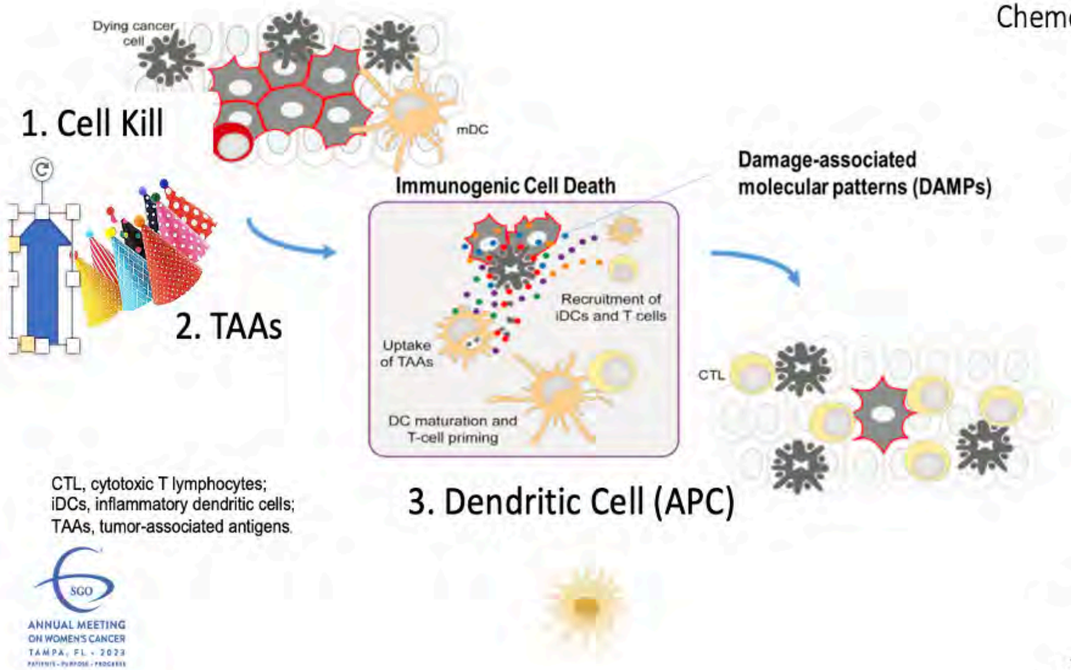
Variable	dMMR EC n = 103	MMRp EC n = 142
ORR % (95% CI)	**46** (34.9-54.8)	**19** (8.3-20.1)
Complete response	11 (10.7)	3 (2.1)
Partial response	35 (34.0)	16 (11.3)
Stable disease	13 (12.6)	31 (21.8)
Progressive disease	39 (37.9)	77 (54.2)
Not evaluable	3 (2.9)	0
Not done	2 (1.9)	15 (10.6)

Marabelle, J Clin Oncol 2020

Courtesy of Dr. Rebecca Arend

In the era of targeted and immunotherapies, how can we improve response to both cytotoxic chemotherapy and immunotherapies?

How can we improve response to checkpoint inhibitors?



Chemotherapy has been shown to:

- Enhance antigen presentation
- Enhance immunogenicity (release of adjuvants by cells)
- Increase susceptibility to immune attack

4. Cytotoxic T cell

Zitvogel L et al. *Immunity*. 2013;39:74-88.

Because of high recurrence rates, a variety of maintenance/ consolidation strategies following completion of first-line chemotherapy have been tested

Courtesy of Dr. Rebecca Arend

GOG FOUNDATION

NRG-GY018

Study Design

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer
- Pathology report showing results of institutional MMR IHC testing
- ECOG PS 0, 1, or 2
- No prior chemo except prior adjuvant chemo if completed ≥12 mo before study

Stratification Factors

- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

N = 816
(591 pMMR,
225 dMMR)

R
1:1

Arm 1
Placebo IV Q3W +
Paclitaxel 175 mg/m² IV Q3W +
Carboplatin AUC 5 IV Q3W

for 6 cycles

→ **Arm 1**
Placebo IV Q6W

for up to 14 additional cycles

Arm 2
Pembrolizumab 200 mg IV Q3W +
Paclitaxel 175 mg/m² IV Q3W +
Carboplatin AUC 5 IV Q3W

for 6 cycles

→ **Arm 2**
Pembrolizumab
400 mg IV Q6W

for up to 14 additional cycles

Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of MMR IHC testing at institution vs centralized

Median follow-up:

- IA1 data cutoff date of December 16, 2022: dMMR cohort, 12 months; pMMR cohort, 7.9 months
- **Current analysis data cutoff date of August 18, 2023**: dMMR cohort, 20.6 months; pMMR cohort, 15.8 months

MADRID 2023 ESMO congress

Ramez N. Eskander

GOG FOUNDATION

ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status
- Prior external pelvic radiotherapy
- Disease status

R1:1

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m² Q3W for 6 cycles

→ **Dostarlimab IV** 1000 mg Q6W up to 3 years[a]

Placebo IV
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m² Q3W for 6 cycles

→ **Placebo IV** Q6W up to 3 years[a]

→ **Follow-up**

Primary endpoints

- PFS by INV per RECIST v1.1
- OS

Secondary endpoints

- PFS by BICR per RECIST v1.1
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

Further study details can be found at Mirza MR, et al. N Engl J Med. 2023 Jun 8;388(23):2145-2158.

[a]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Dr Mansoor Raza Mirza

AtTEnd Study Design

- Endometrial carcinoma or carcinosarcoma
- Patients with advanced (stage III-IV) newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence.
- In recurrent patients, one prior line of systemic platinum-based regimen is permitted with a platinum-free interval ≥ 6 months.
- ECOG 0-2
- Normal organ and bone marrow function

R 2:1

- Paclitaxel 175mg/m² carboplatin AUC 5 or 6 atezolizumab 1200mg → Maintenance atezolizumab 1200mg
- Paclitaxel 175mg/m² carboplatin AUC 5 or 6 placebo → Maintenance placebo

Confirmed PD

Stratified by:

- Country
- Endometrioid vs. other histotypes
- Recurrent disease vs newly diagnosed
- pMMR vs dMMR vs non evaluable *(centrally evaluated)*

Endpoints

Hierarchical order

PFS dMMR	IF POSITIVE	PFS All comers	IF POSITIVE	OS* All comers
α (two-sided) 4%	α=4%	α (two-sided) 4%	α=4%	α (two-sided) 5%
HR: 0.5		HR: 0.7		HR: 0.7

ECOG: Eastern Cooperative Oncology Group. pMMR: mismatch repair proficient. dMMR: mismatch repair deficient. AUC: area under the curve. PD: progressive disease. PFS: Progression free survival. OS: overall survival. HR: hazard ratio.

*OS interim analysis planned with a 63% power

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Nicoletta Colombo, MD

DUO-E study design

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

N=718

R 1:1:1

Stratified by:

- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

	Chemotherapy phase	Maintenance phase
Control	CP* (q3w) + Durvalumab pbo (IV q3w)	Durvalumab pbo (IV q4w) + Olaparib pbo (tablets bid)
Durva	CP* (q3w) + Durvalumab (1120 mg IV q3w)	Durvalumab (1500 mg IV q4w) + Olaparib pbo (tablets bid)
Durva+Ola	CP* (q3w) + Durvalumab (1120 mg IV q3w)	Durvalumab (1500 mg IV q4w) + Olaparib (300 mg tablets bid)

Patients without disease progression

Treatment until disease progression, unacceptable toxicity or other discontinuation criteria were met

Endpoints

Primary

- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary

- OS (analytical)
- Safety

Exploratory

- PFS in Durva+Ola vs durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

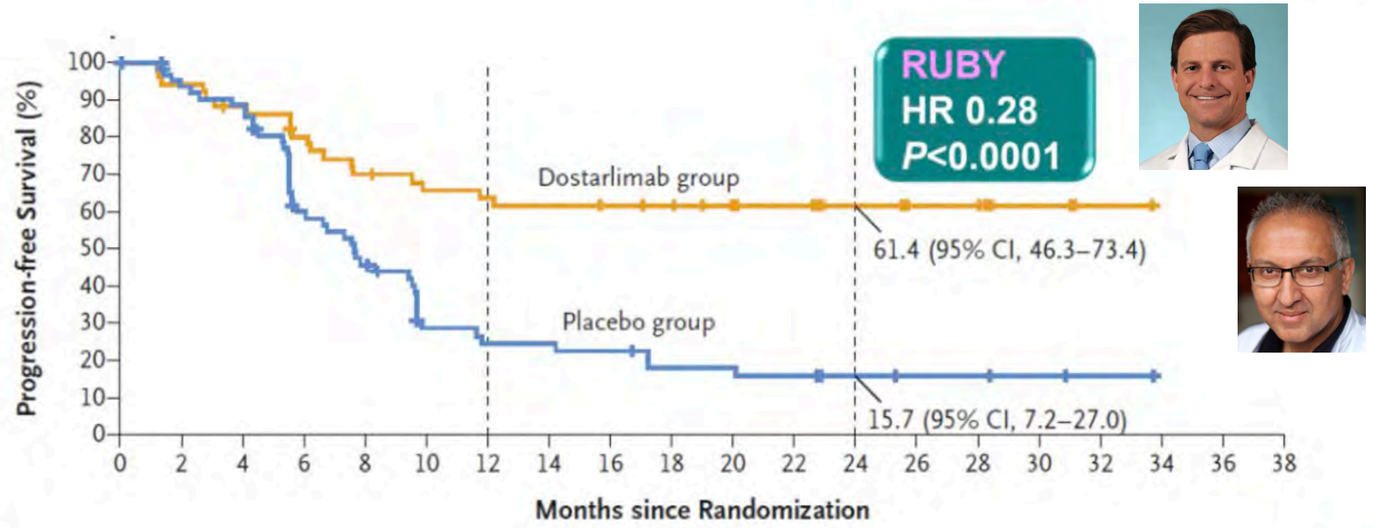
*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.

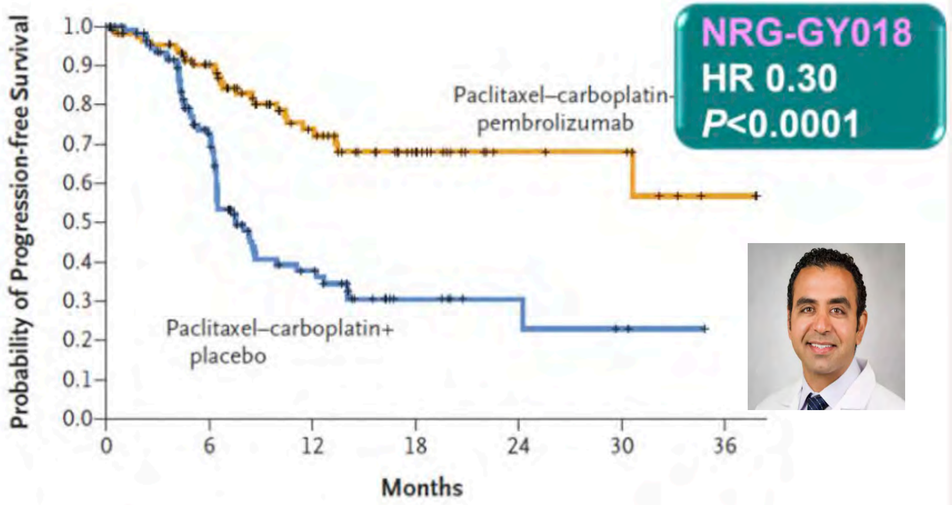
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

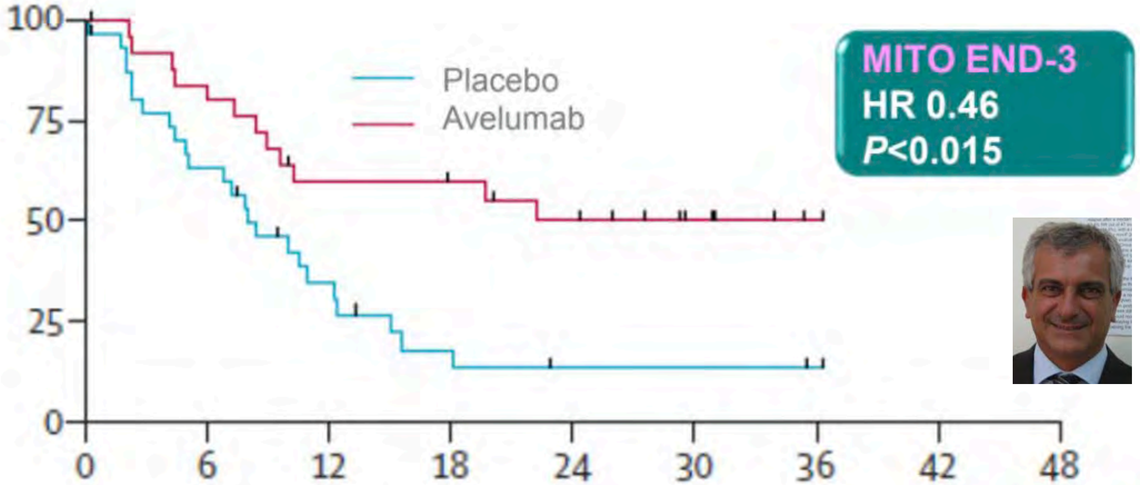
	GY018 (816 pts)	RUBY (494 pts)	AtTEnd (550 pts)	Mito End-3 (125 pts)	Duo-E (718 pts)
Experimental Arm(s) C/P +….	**Pembrolizumab (PD-1)**	**Dostarlimab (PD-1)**	**Atezolizumab (PDL1)**	**Avelumab (PDL1)**	**Durvalumab (PDL1) +/- olaparib (PARPi)**
Study design; primary endpoint	**RP3; PFS in parallel dMMR & pMMR cohorts**	**RP3; PFS and OS**	**RP3; PFS and OS**	**RP2; PFS**	**RP3; PFS in Durva v. Control PFS in Duva+Ola v. Control**
Measurable or evaluable Stage III/IV	YES	YES	YES	YES	YES
Non-measurable Stage IVB	YES	YES		NO	YES
Serous, Clear-Cell, Mixed Histologies	YES	YES	YES	YES	YES
Carcinosarcoma	NO	YES	YES	NO	YES
Recurrent Disease (%)	YES	YES	YES	NO	YES
Performance Status	0-2	0-1	0-2	0-1	0-1
Prior Radiation	YES	YES	YES	YES	YES
Prior Chemotherapy	YES	YES	YES	YES	YES
Time Since Adjuvant Chemo	≥12 months	≥6 months	≥6 months	≥6 months	≥12 months
Duration of maintenance therapy	14 cycles (~2 years)	3 years	Disease progression, toxicity, or other indication	Disease progression, toxicity, or other indication	Disease progression, toxicity, or other indication

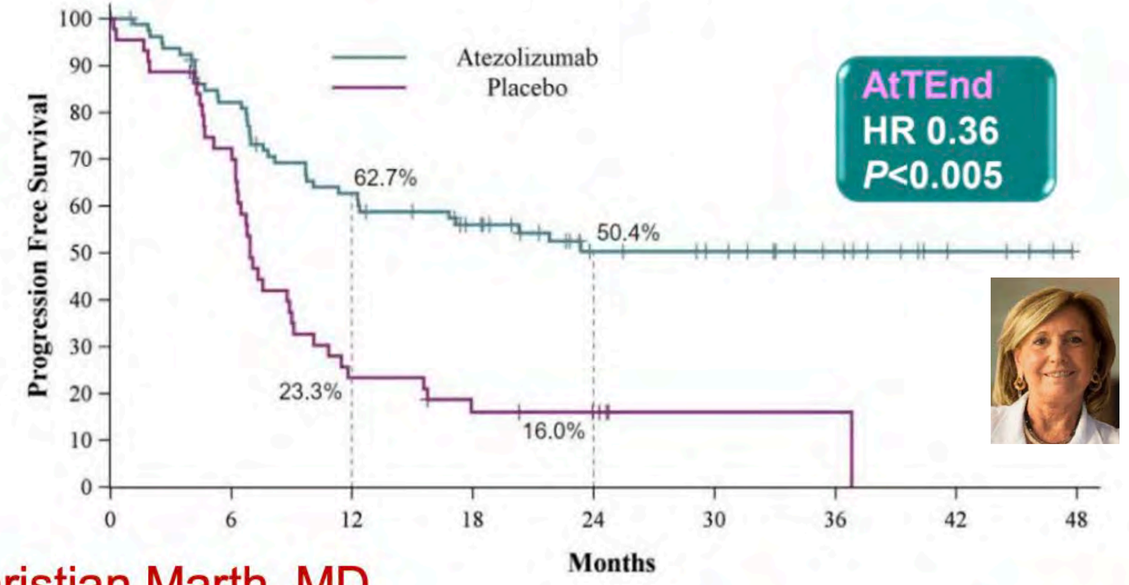
Modified from Drs Arend and Backes

Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in **dMMR** Tumors





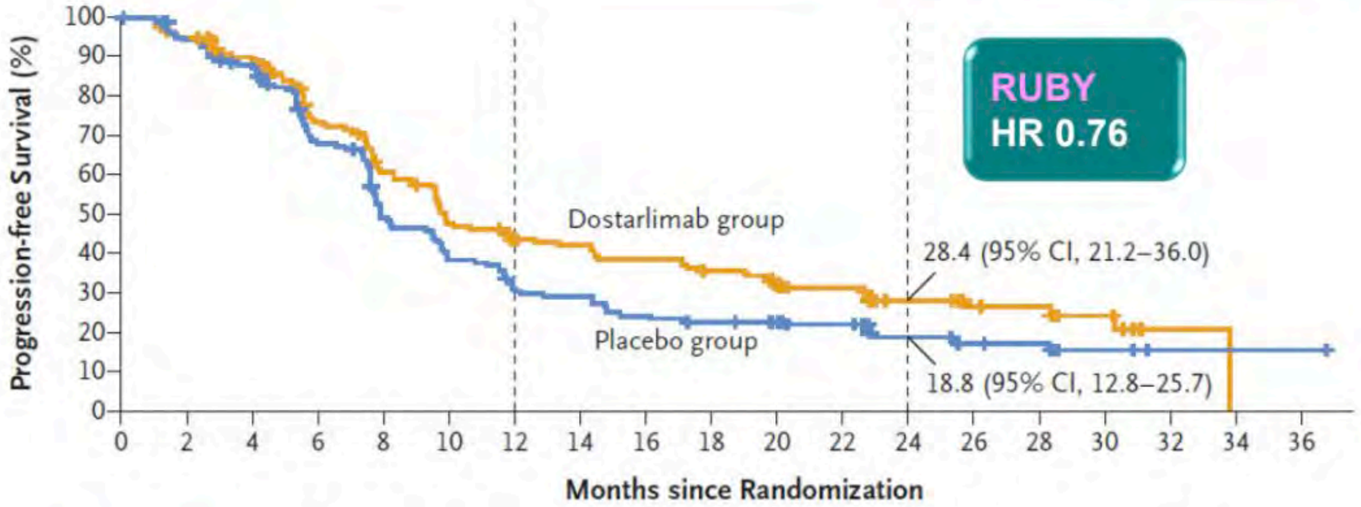




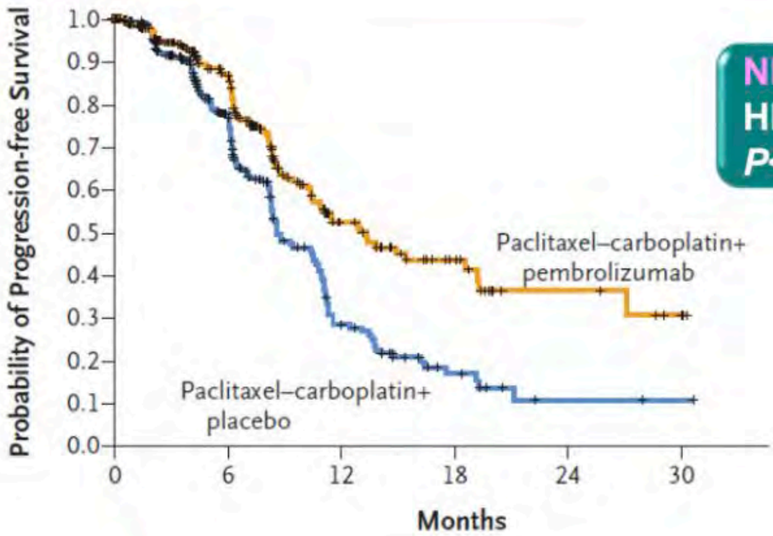
Courtesy of Christian Marth, MD

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Sandro Pignata et al. The Lancet Oncology 2023, Nicoletta Colombo et al. ESMO 2023

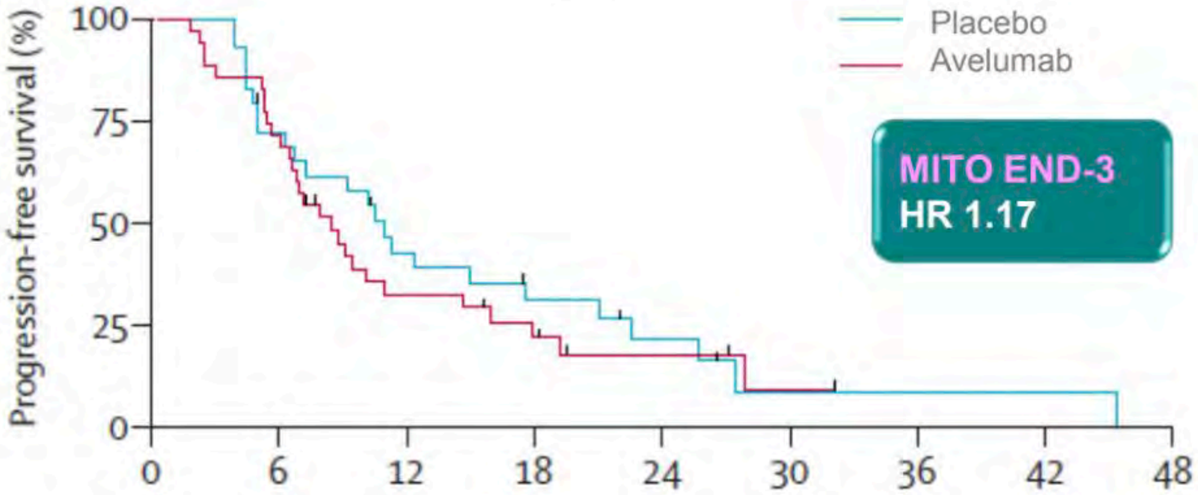
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in **pMMR** Tumors



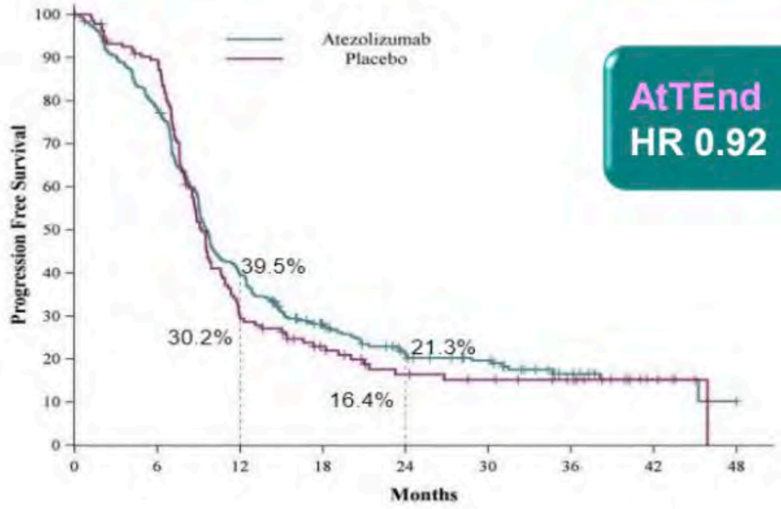
RUBY
HR 0.76



NRG-GY018
HR 0.54
***P*<0.0001**



MITO END-3
HR 1.17



AtTEnd
HR 0.92

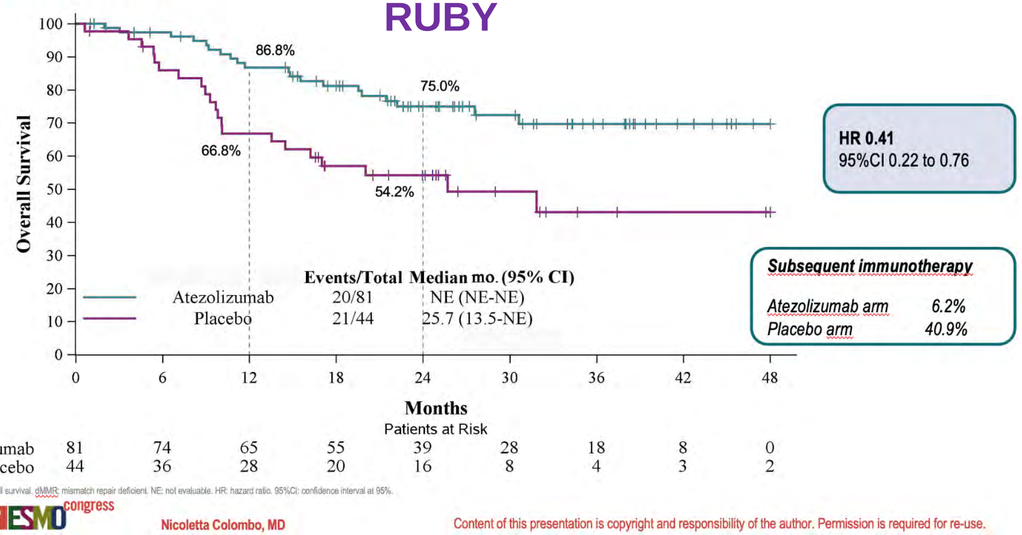
Courtesy of Christian Marth, MD

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Sandro Pignata et al. The Lancet Oncology 2023, Nicoletta Colombo et al., ESMO 2023

OS Data: No benefit in All Comers- Ruby, AtTEnd, Mito End-3

OS in dMMR

RUBY



OS: overall survival. dMMR: mismatch repair deficient. NE: not evaluable. HR: hazard ratio. 95%CI: confidence interval at 95%.

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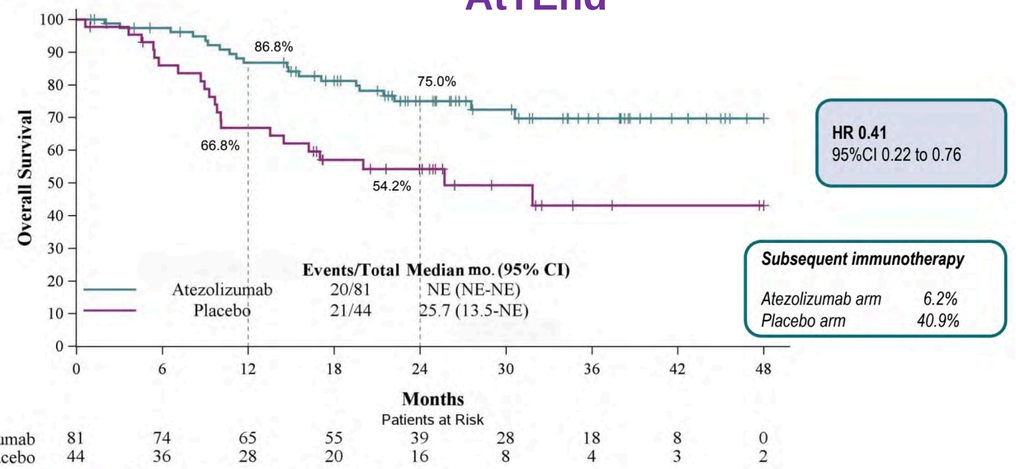
OS in dMMR

AtTEnd



OS: overall survival. dMMR: mismatch repair deficient. NE: not evaluable. HR: hazard ratio. 95%CI: confidence interval at 95%.

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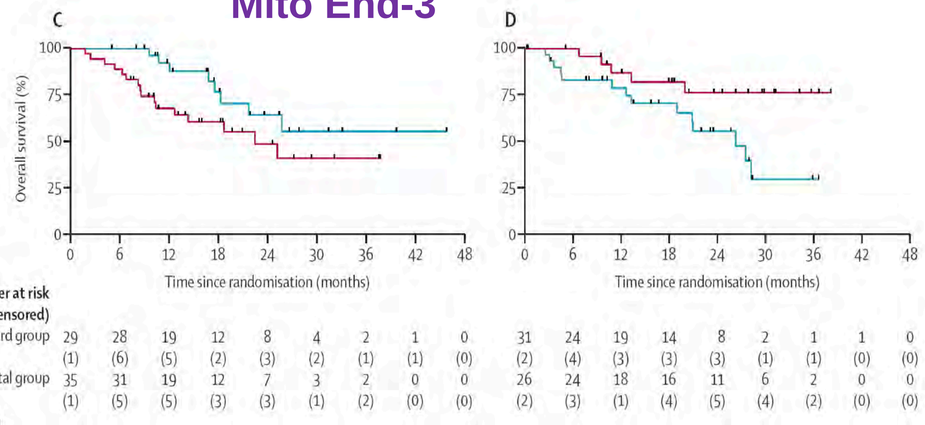
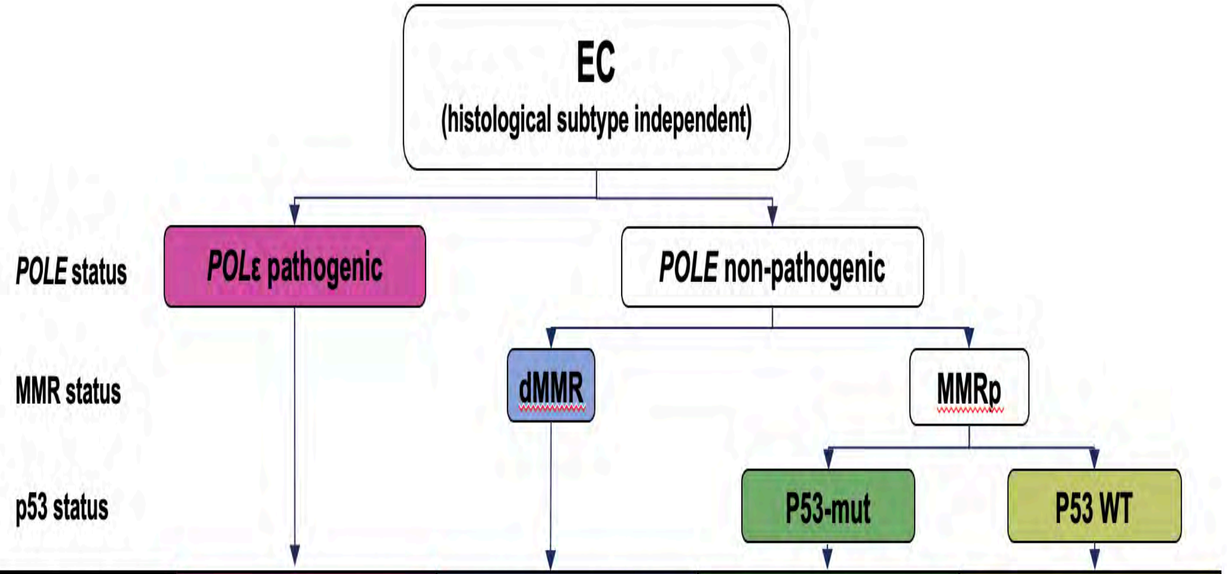
Mito End-3



GOG FOUNDATION

RUBY Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients



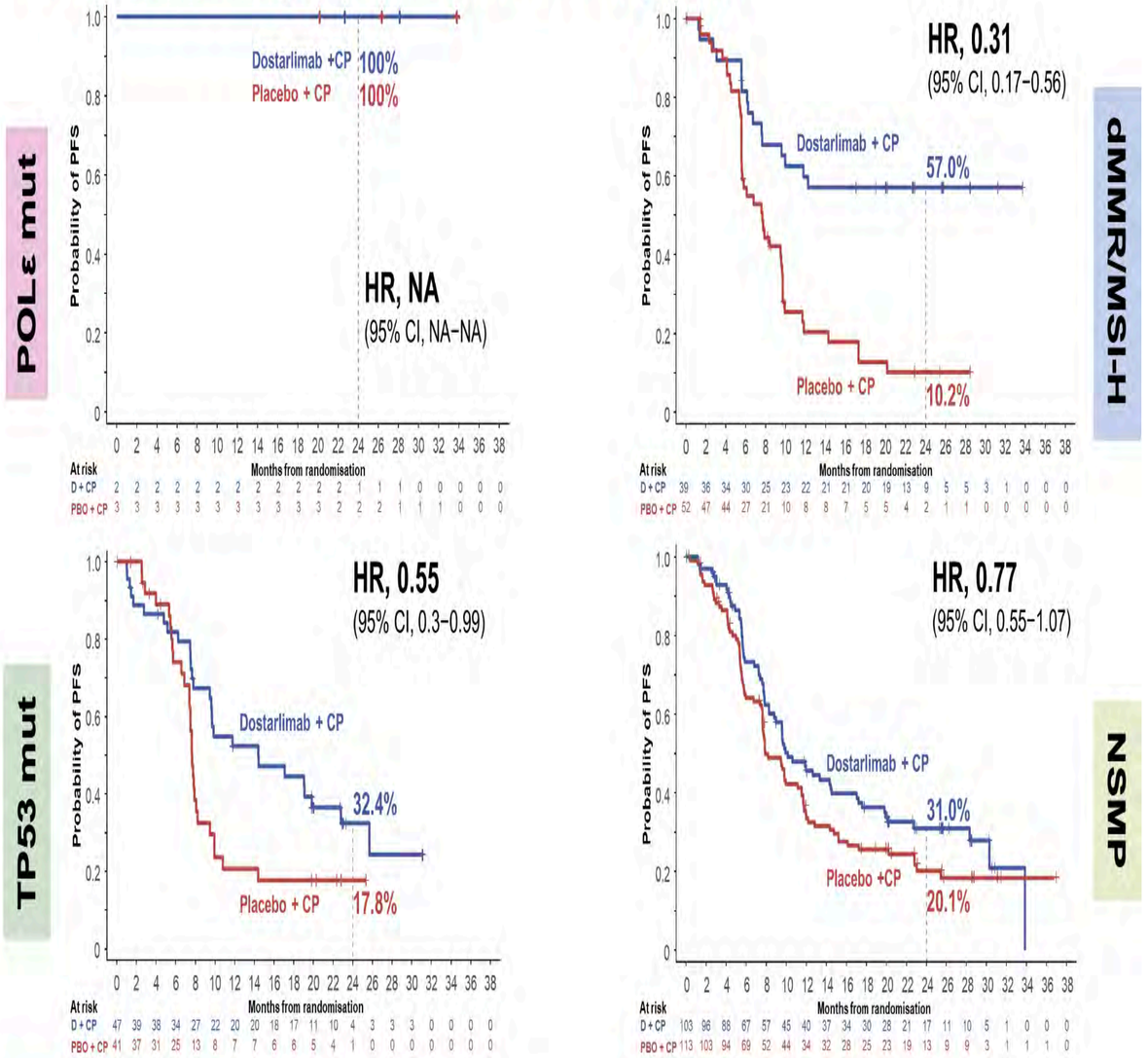
Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

Efficacy per molecular classification was an exploratory analysis.

dMMR, mismatch repair deficient; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε , polymerase epsilon; SCNA, somatic copy number alterations; TIL, tumor-infiltrating lymphocytes; TLS, tertiary lymphoid structures; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

Dr Mansoor Raza Mirza

PFS According to Molecular Subgroup

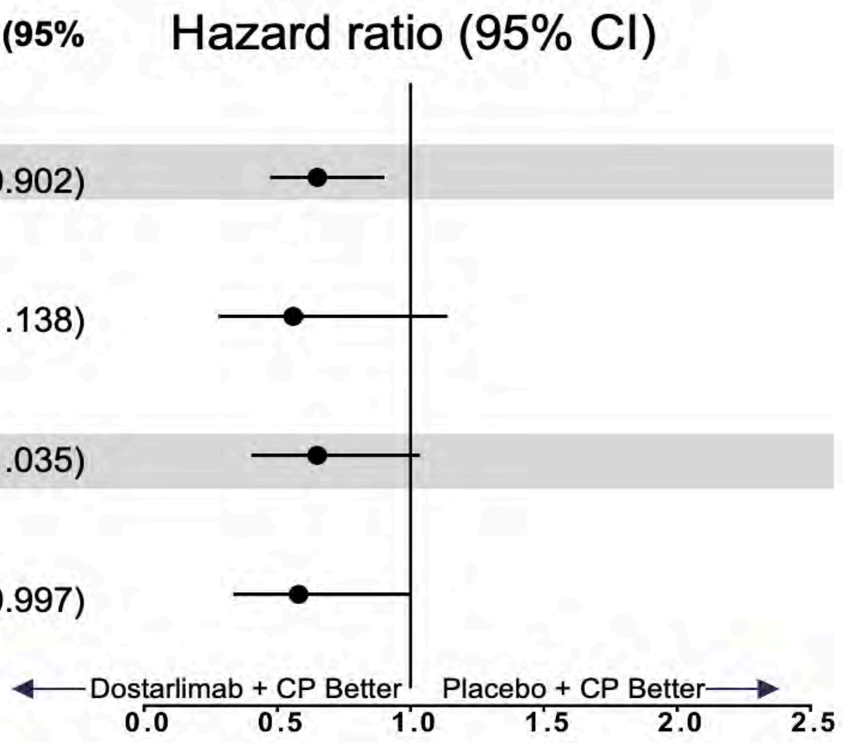


Data based on exploratory analysis based on 400 patients from the RUBY trial with known molecular classification with whole exome sequencing.

CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NR, not reached; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; POLε , polymerase epsilon; TP53, tumor protein 53.

Consistent PFS Benefit in Histological Subgroups

Histology	Dostarlimab + carboplatin-paclitaxel (no. of events/no. of patients)	Placebo + carboplatin-paclitaxel (no. of events/no. of patients)	Hazard ratio (95% CI)
Endometrioid carcinoma	64/130	89/136	0.65 (0.473–0.902)
Carcinosarcoma	14/24	18/22	0.56 (0.278–1.138)
Serous adenocarcinoma	36/55	35/48	0.65 (0.403–1.035)
Other	21/36	35/43	0.58 (0.335–0.997)



Hazard ratios are based on unstratified Cox regression model.
CP, carboplatin-paclitaxel; HR, hazard ratio; PFS, progression-free survival.

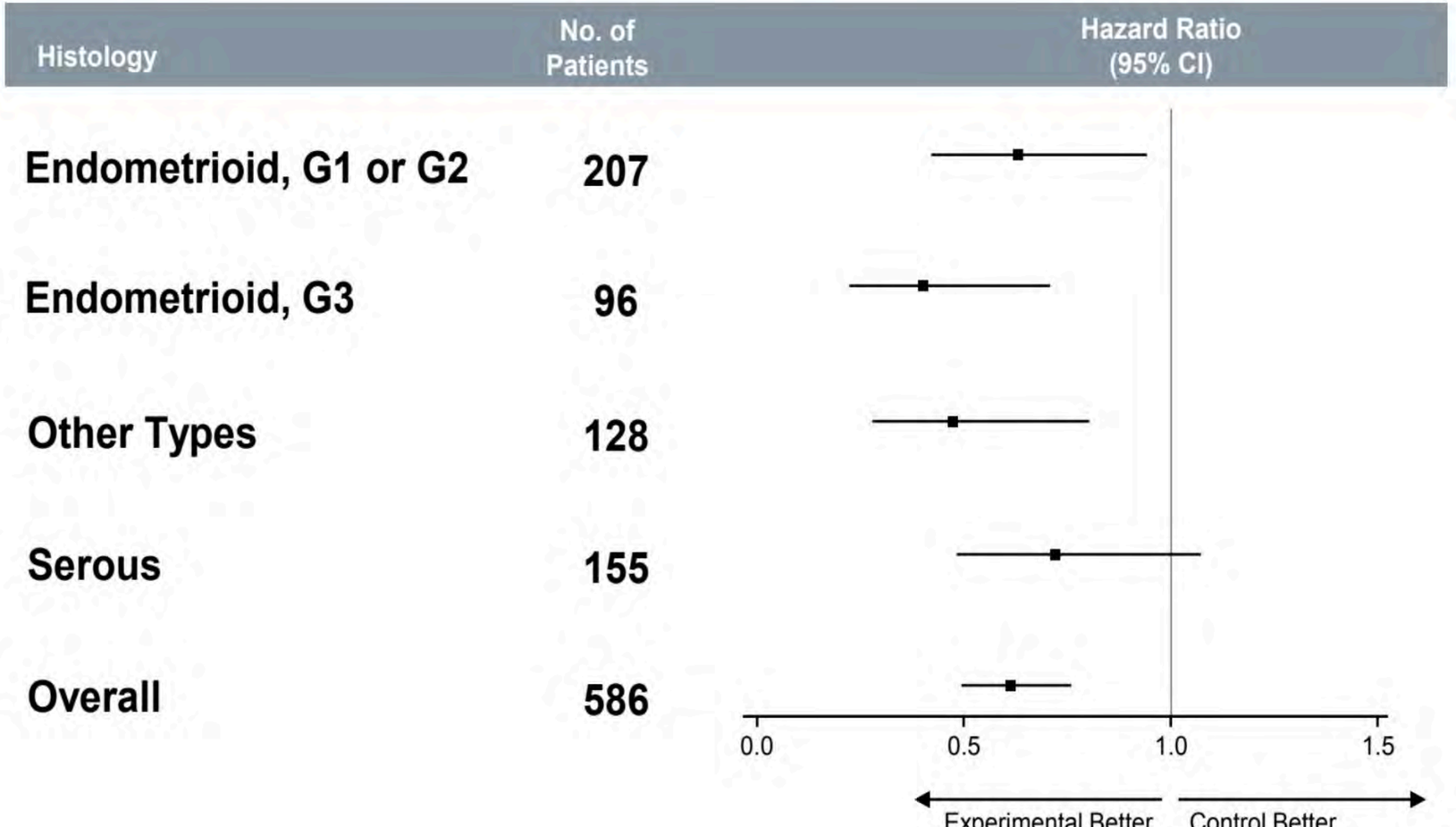
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – Subgroup Analyses of PFS

PFS per RECIST v1.1 in pMMR Population

PFS by Histology in pMMR Population

Efficacy curves in the two MMR cohorts separated early in treatment, with a preserved separation throughout the evaluation period.

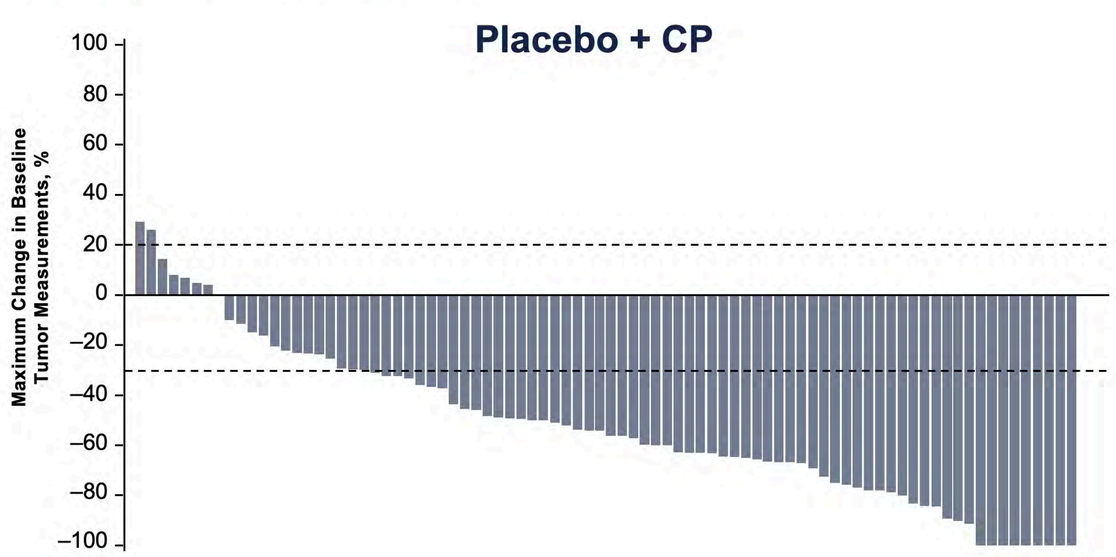
Benefit was observed in most subgroups, including among patients who had received previous adjuvant chemotherapy or radiation, among those with less common histologic subtypes and in patients who identify as Black or White.



Data cutoff: December 16, 2022.
Eskander R, et al. SGO 2023. Abstr

Durability of Response in Patients on GY018-Placebo

Central dMMR Waterfall Plot



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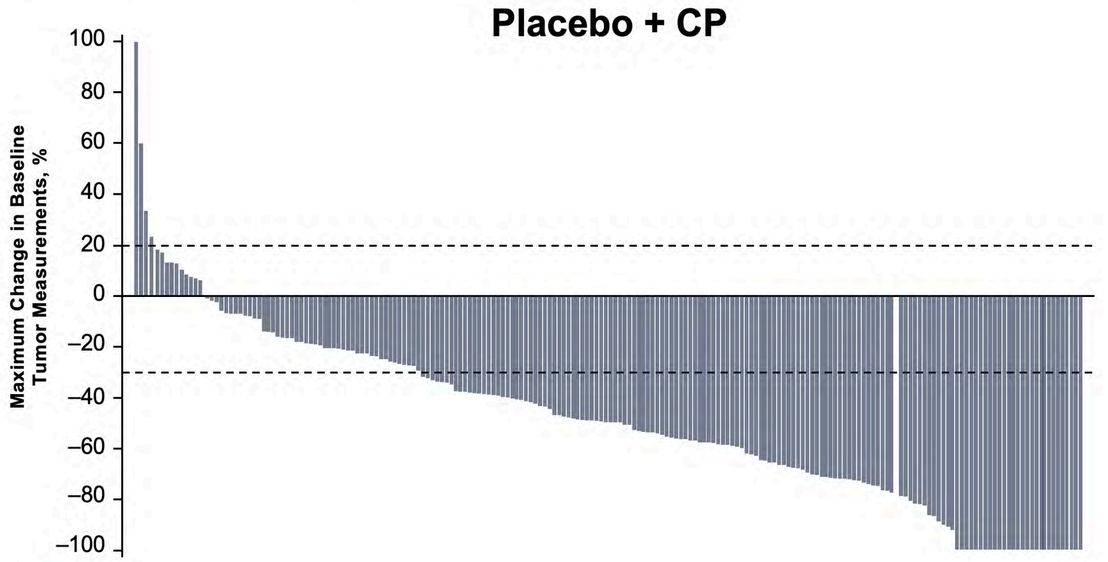
Data cutoff date: August 18, 2023.

Central pMMR Waterfall Plot



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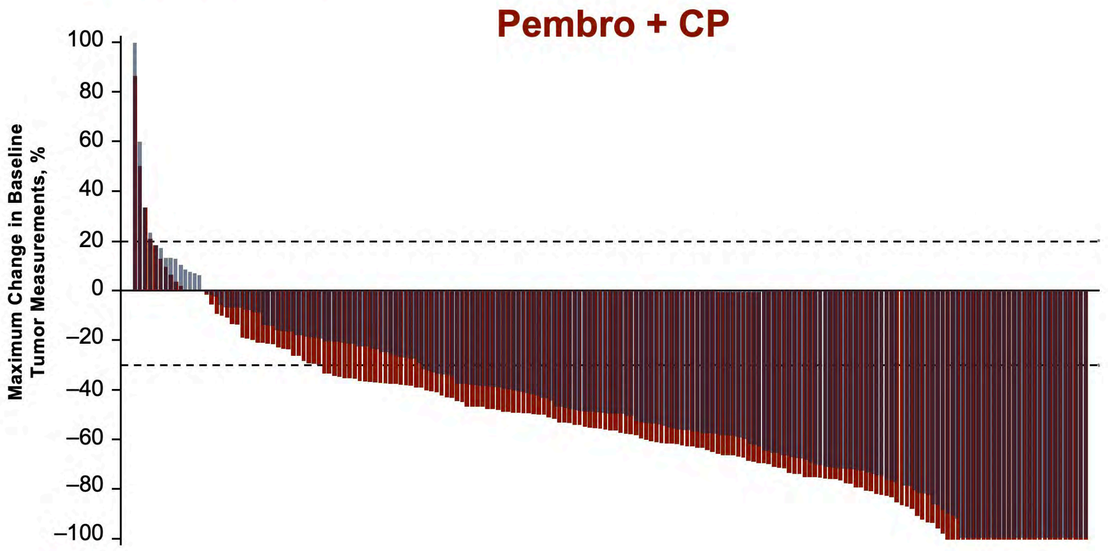
Durability of Response in Patients on GY018-Pembrolizumab

Central pMMR Waterfall Plot



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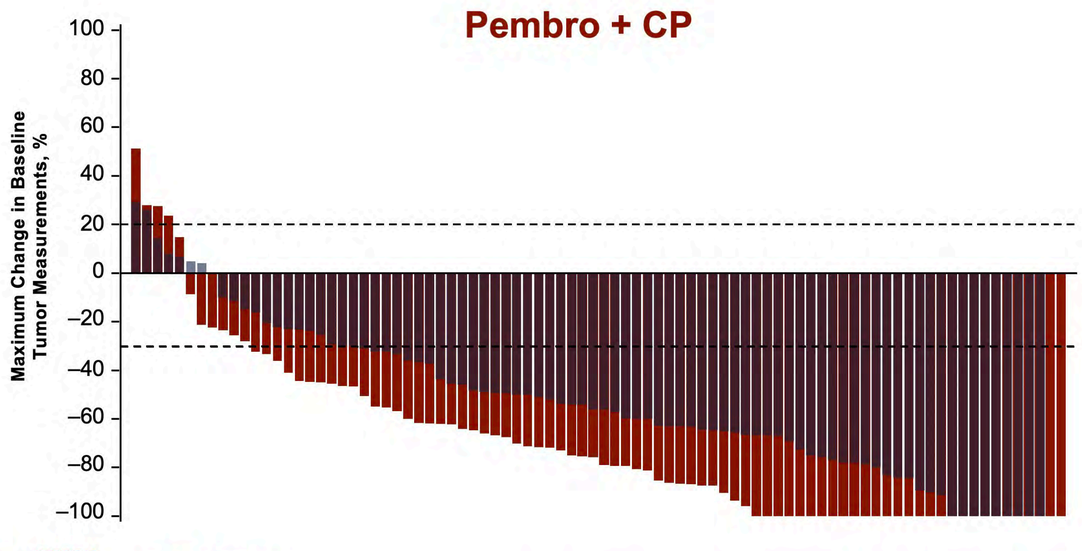
Central dMMR Waterfall Plot



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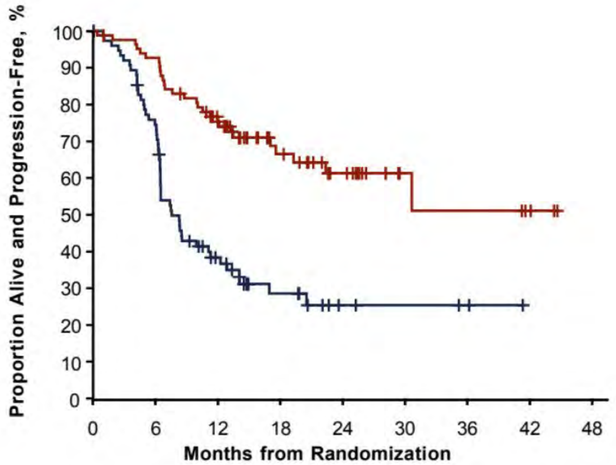
NRG-GY018 Ad hoc Analyses

PFS by Methylation Status in dMMR Population

Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	51/77	7.5 (6.4–11.3)	0.307 (0.19–0.49) *P* <0.0001
Pembro + CP	28/83	NR (22.3–NR)	

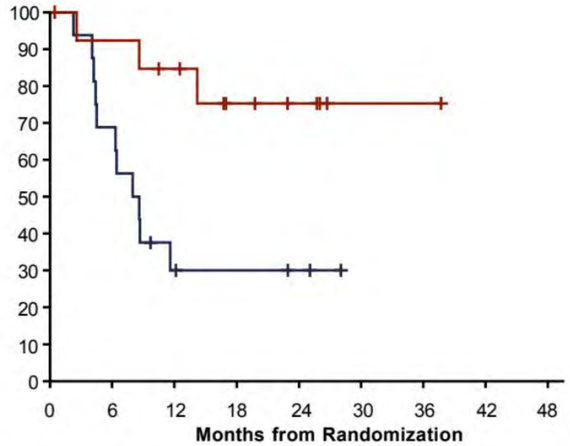


Number at risk (Cumulative number censored)

Placebo + CP	77 (2)	55 (3)	23 (9)	11 (16)	4 (22)	3 (23)	2 (24)	0 (26)
Pembro + CP	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52) 0 (55)

No Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	11/17	8.3 (4.4–NR)	0.263 (0.07–0.99) *P* = 0.0172
Pembro + CP	3/13	NR (14.2–NR)	

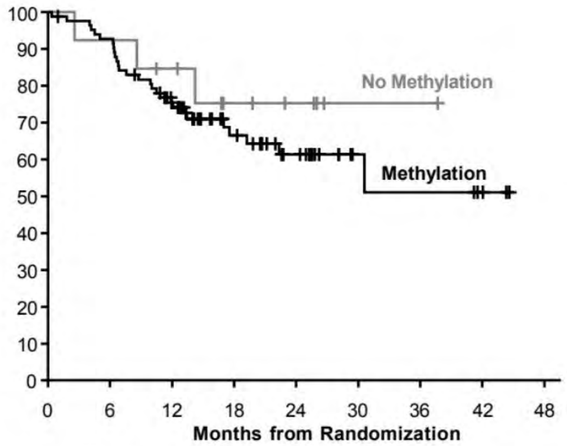


Number at risk (Cumulative number censored)

Placebo + CP	17 (0)	11 (1)	4 (2)	3 (3)	2 (4)	0 (6)		
Pembro + CP	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)

Methylation Status
Pembro + CP Arm

	Events n/N	Median (95% CI), mo
No Methylation	3/13	NR (14.2–NR)
Methylation	28/83	NR (22.3–NR)



Number at risk (Cumulative number censored)

No Methylation	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)
Methylation	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52) 0 (55)

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Ramez N. Eskander

Data cutoff date: August 18, 2023.

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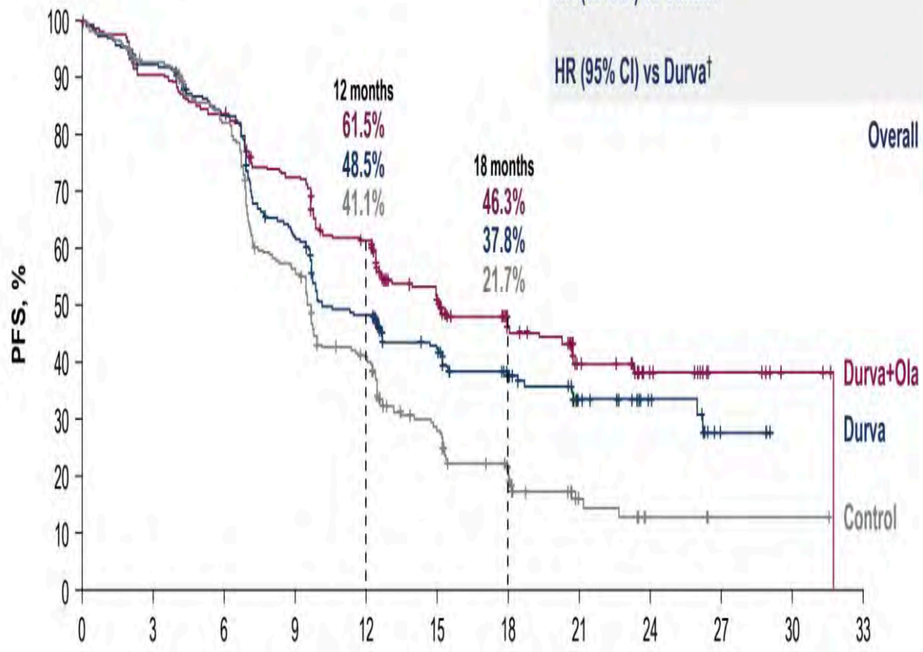
DUO-E

PFS: ITT population

Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk												
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

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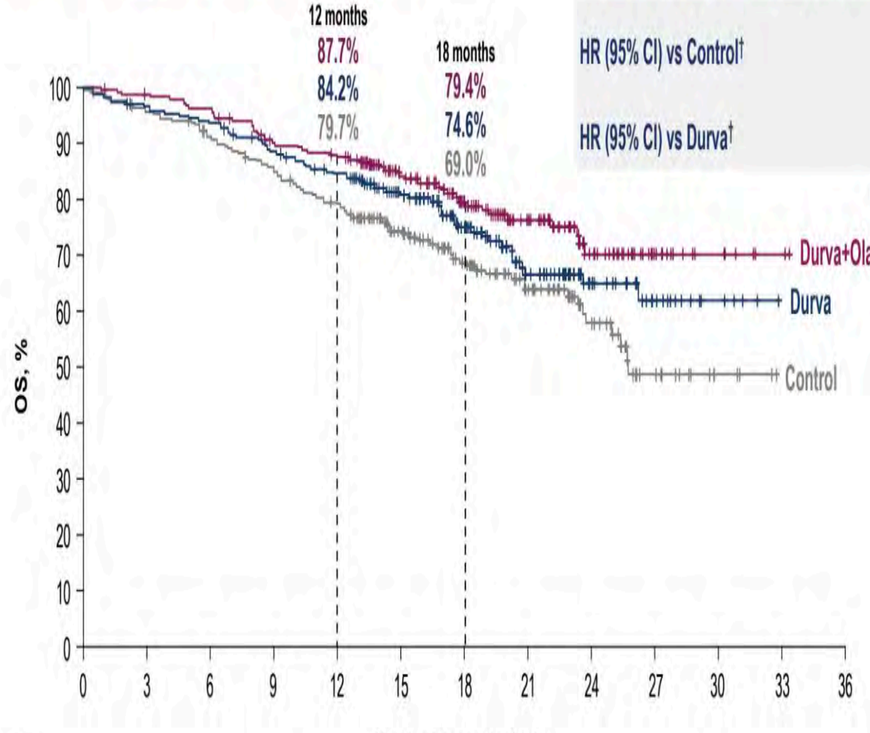
OS: ITT population

Secondary endpoint; interim analysis

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI),* months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs Control†		**0.77** (0.56–1.07); *P*=0.120	**0.59** (0.42–0.83); *P*=0.003
HR (95% CI) vs Durva†			**0.77** (0.53–1.10)

Overall data maturity 27.7%



No. at risk												
Durva+Ola	239	233	227	208	202	152	109	77	38	18	8	2	0
Durva	238	227	221	205	192	147	105	64	34	17	6	0	0
Control	241	229	215	201	185	136	104	69	35	15	4	0	0

The median (range) duration of follow-up for OS was 18.6 (0.5–32.9), 18.4 (2.1–33.0), and 18.7 (1.1–33.4) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. OS rates were estimated by the KM method. *CI for median OS is derived based on the Brookmeyer–Crowley method; †The HRs were estimated from an unstratified Cox proportional hazards model. The CI was calculated using a profile likelihood approach. *P* values were calculated using an unstratified log-rank test. *P* values failed to reach statistical significance. NR, not reached.

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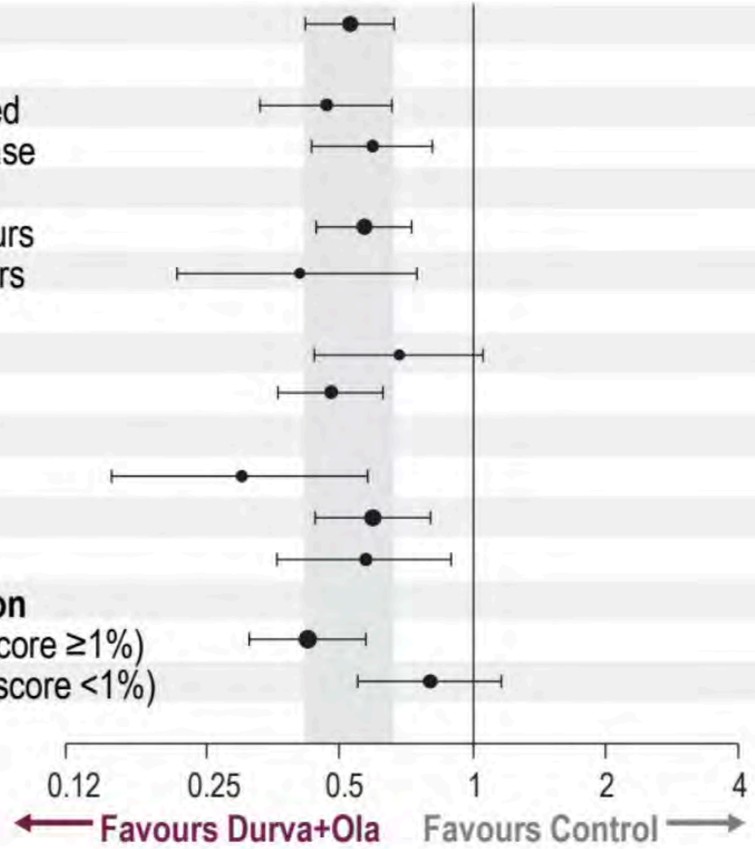
Subgroup analysis of PFS: Durva+Ola vs Control

By stratification factors and biomarker status



	HR (95% CI)	Durva+Ola n/N (%)	Control n/N (%)
All patients	0.53 (0.42–0.67)	126/239 (52.7)	173/241 (71.8)
Disease status			
Newly diagnosed	0.47 (0.33–0.66)	58/114 (50.9)	81/115 (70.4)
Recurrent disease	0.59 (0.43–0.81)	68/125 (54.4)	92/126 (73.0)
MMR status			
Proficient tumours	0.57 (0.44–0.73)	108/191 (56.5)	148/192 (77.1)
Deficient tumours	0.41 (0.21–0.75)	18/48 (37.5)	25/49 (51.0)
Region			
Asia	0.68 (0.44–1.06)	37/67 (55.2)	45/68 (66.2)
Non-Asia	0.48 (0.36–0.63)	89/172 (51.7)	128/173 (74.0)
HRRm status			
HRRm	0.30 (0.15–0.58)	16/39 (41.0)	23/32 (71.9)
Non-HRRm	0.59 (0.44–0.80)	81/141 (57.4)	96/132 (72.7)
Unknown	0.57 (0.36–0.89)	29/59 (49.2)	54/77 (70.1)
PD-L1 expression			
Positive (TAP score ≥1%)	0.42 (0.31–0.57)	68/150 (45.3)	114/163 (69.9)
Negative (TAP score <1%)	0.80 (0.55–1.16)	55/82 (67.1)	57/75 (76.0)
Unknown	NC (NC–NC)	3/7 (42.9)	2/3 (66.7)

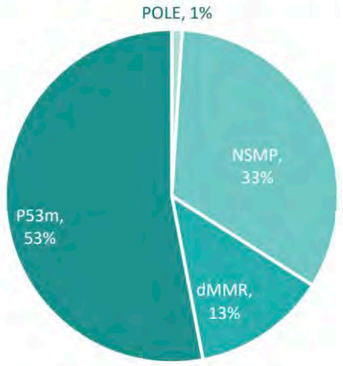
Stratification factors (disease status, MMR status, and geographic region) are per the randomisation code. PD-L1 status in baseline tumour tissue was determined centrally using Ventana PD-L1 SP263 immunohistochemistry assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumour area populated by tumour cells or immune cells with membranous PD-L1 staining. HRRm status was assessed in baseline tumour tissue using the Foundation One CDx NGS assay and includes a mutation in any of these genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing.

Background – Rational

- Advanced and metastatic (M+) EC is an heterogeneous tumor [1,2]
- Many of advanced EC tumors have significant deficiencies in DNA repair pathways
- P53 mutations are associated with high Copy Number Alterations (CNA) [3]
- Homologous replication deficiency (HRD) is significantly associated with P53 mutated EC [4]

➔ Frequent high DNA damage suggests the possibility to use PARP inhibitors as maintenance after chemotherapy

Molecular repartition in advanced/M+ EC



Joly et al, ESGO 2022 From Utola population

UTOLA study design

GINECO

Randomized phase II trial

INDICATION OF CHEMOTHERAPY
(according to physician decision)

ADVANCED OR METASTATIC ENDOMETRIAL CANCER

Endometrioid, clear cells, serous and mixed histologies

Adjuvant CT allowed (if > 1 yr)

→ **Platinum based CT***

6 cycles

→ **NED CR PR SD**

→ **Inclusion = 2 years**

R

n=147

2:1

→ **Olaparib maintenance** n=98

→ **Placebo maintenance** n=49

Until PD (RECIST 1.1)

Chemotherapy, at least **4 cycles*
*Recommended regimen : **Carboplatin plus Paclitaxel***

Stratification factors
- P53 and MMR status
- Response to previous CT

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UTOLA objectives

GINECO

Objectives	Endpoints
Primary endpoint : PFS in the ITT Population	Endpoint : Improvement of median PFS from 4.5 months to 7.5 months (from randomization)
Main secondary endpoints	• PFS according to P53 status • PFS according to response rate • OS in ITT and according to P53 status • Safety • (QoL)
Pre-specified other secondary endpoint	PFS according to HRD status

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Joly-Lobbdez ESMO 2023

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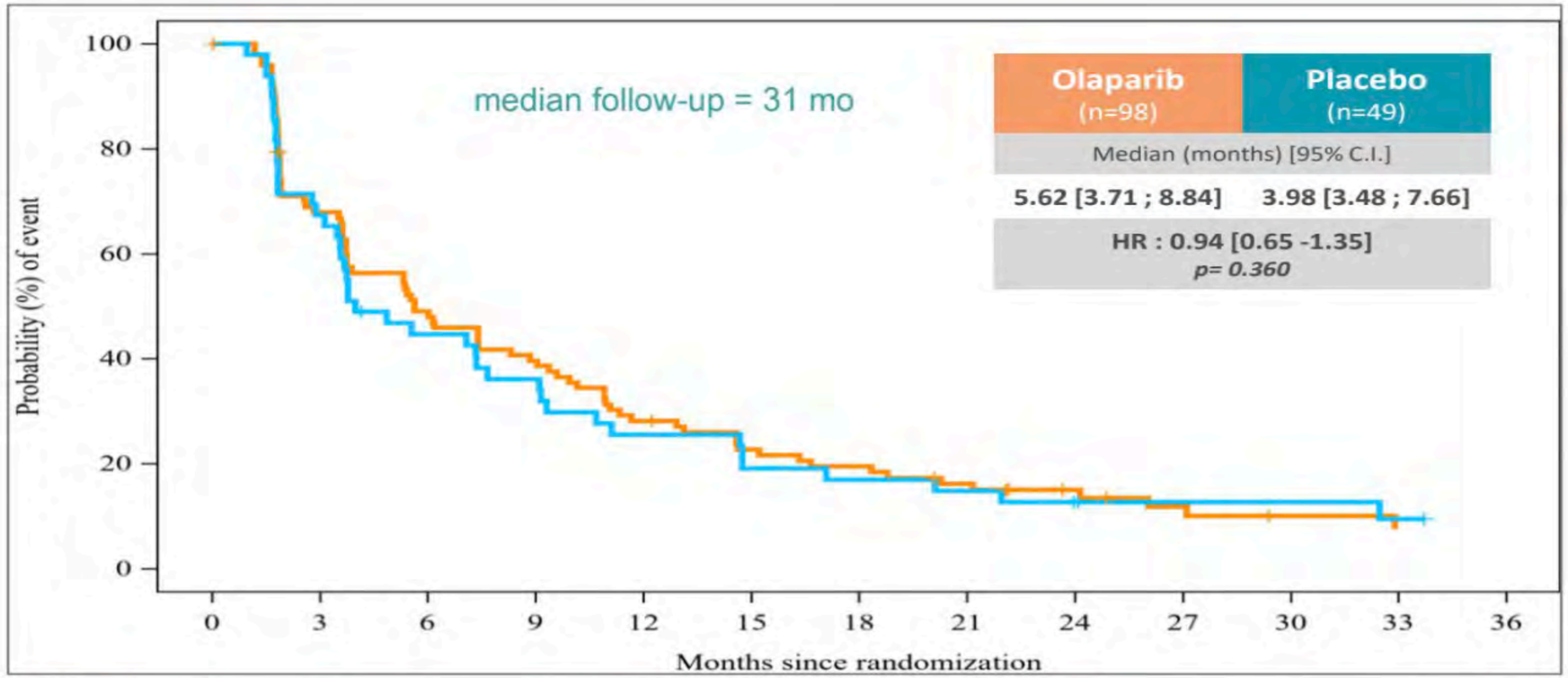
Utola PFS: ITT

PFS* by investigator assessment: ITT

N=147



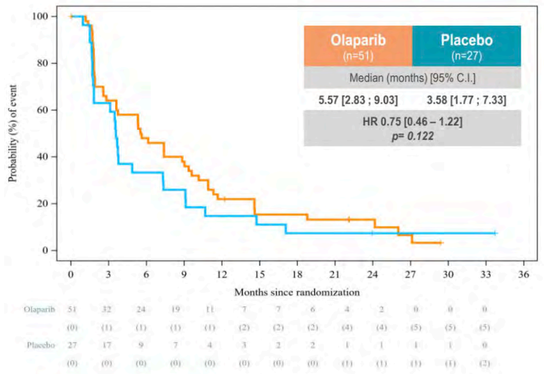
Olaparib	98	65	47	38	27	21	18	14	10	7	4	3	3
	(0)	(2)	(2)	(2)	(2)	(3)	(3)	(4)	(7)	(8)	(10)	(10)	(10)
Placebo	49	33	21	17	12	9	8	7	5	4	4	3	2
	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(3)	(3)	(3)	(4)

PFS calculated from randomization (end of CT)

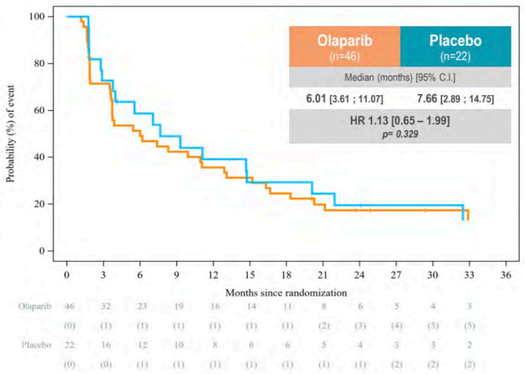
Utola PFS by p53, HRD, or Both

PFS by investigator assessment : P53 status

P53 mut – n= 78



P53 WT – n= 68



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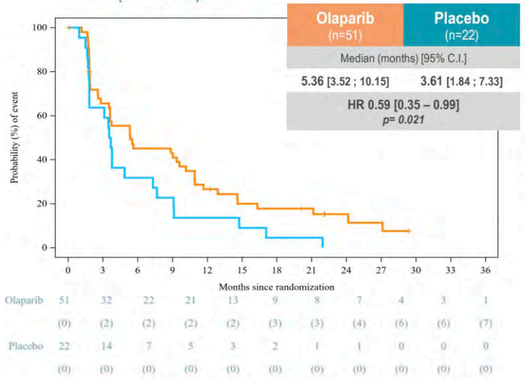
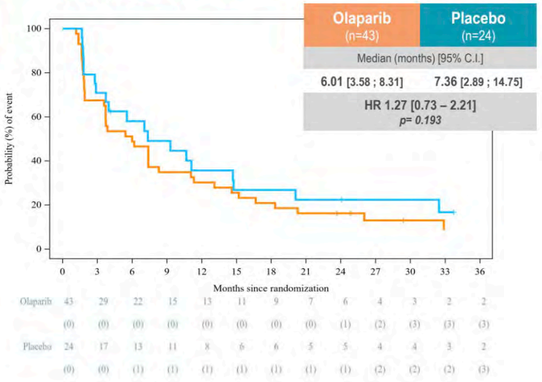
PFS: According to HRD status

HRD (LGE ≥6) n = 73



HRp (LGE <6) n = 67



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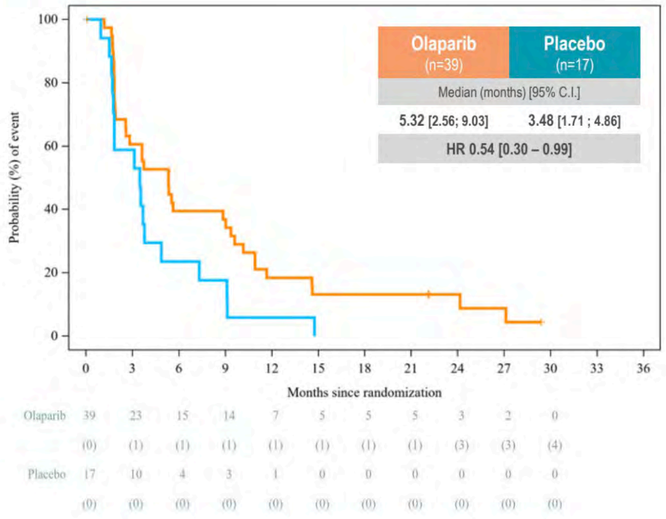
PFS: HRD (LGE ≥6) and P53mut (exploratory analysis)

LGE ≥6, pMMR, P53 mut n=56



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ENGOT-en9/A-AGO: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Persistent, Recurrent, or Metastatic Endometrial Carcinoma (LEAP-001)

Model C

- Stage III, IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients

1:1 R

Pembrolizumab 200 mg IV infusion Q3W15 mg/kg q3w

Up to 35 infusions

Lenvatinib 20mg orally QD

Up to 7 cycles

Carboplatin AUC 6 (-5) IV infusion Q3W

Up to 7 cycles

Paclitaxel 175 mg/m² IV infusion Q3W

Stratify:

- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - EGOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)

ENGOT
European Network of Gynaecological Oncological Trial groups

Christian Marth et al. Int J Gynecol Cancer 2021

Frauenheilkunde Innsbruck

MERCK

001 Trial Evaluating KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) as First-Line Treatment for Patients with Advanced or Recurrent Endometrial Carcinoma

RAHWAY, N.J., & NUTLEY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and Eisai today announced that the Phase 3 LEAP-001 trial evaluating KEYTRUDA, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, did not meet its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) for the first-line treatment of patients with advanced or recurrent endometrial carcinoma whose disease is mismatch repair proficient (pMMR)/not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)/MSI-H.

At the final analysis, KEYTRUDA plus LENVIMA did not improve OS or PFS sufficiently to meet the study's prespecified statistical criteria in the first-line treatment of certain patients with advanced or recurrent endometrial carcinoma versus a standard of care, platinum-based chemotherapy doublet (carboplatin plus paclitaxel). The safety profile of KEYTRUDA plus LENVIMA was consistent with that observed in previously reported studies evaluating the combination. A full evaluation of the data from this study is ongoing. The companies will work with investigators to share the results with the scientific community.

KEYNOTE-C93/GOG-3064/ENGOT-en15: A phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma.

Phase 3 KEYNOTE C93: First-Line Pembrolizumab vs Chemotherapy in dMMR[1]

- Histologically confirmed stage III/IV recurrent EC including carcinosarcoma
- ECOG PS 0/1
- No prior systemic therapy
- dMMR

Stratification
- Disease status (newly diagnosed advanced EC vs recurrent EC)
- Histology (endometrioid vs nonendometrioid)

R

N = 350

Pembrolizumab
400 mg IV Q6W

Paclitaxel
175 mg/m² IV Q3W
+
Carboplatin
AUC 6 IV Q3W

- **Primary endpoints:** PFS, OS
- **Secondary endpoints:** ORR, DCR, DOR

Courtesy of Shannon Westin, MD

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Summary

- Remarkable progress in treatment of upfront advanced/first-line recurrent endometrial cancer (EC) based on advancements in molecular understanding and development of novel drugs that target specific tumoral mutations/aberrations and protein expression levels

- Carboplatin/paclitaxel remains an important backbone of treatment for advanced/recurrent disease
  - Only moderate and limited effectiveness, associated with relatively short PFS and high, unsalvagable recurrence rates
  - Escalation/add-on trial strategies appropriate in this setting, especially when treating patients with pMMR, HER2 expressed/amplified, or p53 aberrant disease

- Endometrial cancer has great genomic heterogeneity
- Molecular profiling of EC tumors allows GYN and medical oncologists to realize the promise of precision-based medicine-several molecular biomarkers are prognostic and predictive
  - Test all patients and test early!
  - Targeted therapy options based upon mismatch repair status and HER2
  - Emerging therapeutic options for p53 aberrant v wildtype tumors and HRD positive EC
  - Will molecular testing also allow for smarter radiation therapy strategies?

- Ongoing and future trials will help clarify optimal treatment

Thank you

- GOG-F, Dr. Tom Herzog, Ms. Jenna Cummins, Ms. Cori Niskala, Ms. Lindsey Moeller
- Dr. Angeles Alvarez Secord
- Our patients
- All trial investigators, local trial PIs, colleagues enrolling

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